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(54) Title: COMBINATION OF ADRENERGIC AGONIST AND NMDA ANTAGONIST FOR RELIEVING CHRONIC PAIN WITHOUT ADVERSE SIDE EFFECTS

(57) Abstract: A combination of two drugs, from different and unrelated categories, provides effective and long-lasting relief from neuropathic pain and other chronic or intractable pain. Both drugs can be taken in a painless non-invasive manner, such as by means of pills or skin patches. One drug is an α2 adrenergic agonist, exemplified by clonidine. These agents reduce blood pressure and have sedative-hypnotic effects; those are unwanted side effects in a chronic daily treatment for pain. The other drug is an NMDA antagonist which can be described as mild, minimally toxic, and/or inherently safe (or safened). Three such classes of drugs have been shown to work exceptionally well, with clonidine, in reducing neuropathic pain for prolonged periods: (1) aryl-cyclo-alkanolamine drugs such as procyclidine and biperiden; (2) tricyclo-alkylamine drugs such as ethopropazine; and (3) adamantane derivatives such as memantine. None of these drugs, by itself, can provide effective relief for neuropathic pain; at doses required to provide short-term relief, they cause adverse side effects, and any pain relief they provide is relatively brief. However, when combined with an α2 adrenergic agonist, the two drugs potentiate one another's pain-relieving action, and provide potent and sustained relief, even when each drug is administered at a low dosage that is below its threshold for causing adverse side effects.

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COMBINATION OF ADRENERGIC AGONIST AND NMDA ANTAGONIST FOR RELIEVING CHRONIC PAIN WITHOUT ADVERSE SIDE EFFECTS

BACKGROUND OF THE INVENTION

The present invention relates to neurology and pharmacology, and to drugs which can treat and control various types of chronic pain (including neuropathic pain) without causing adverse side effects.

Available drug treatments for chronic and severe pain are subject to various limitations and shortcomings. Drugs such as ibuprofen, naproxen, acetaminophen, and aspirin do not have nearly the same potency as opiates, such as morphine. Opiates are powerful, but they pose high risks of dependence and addiction, and they cause serious side effects, including drowsiness, gastrointestinal disorders, sexual dysfunctions, etc.

In addition, opiates are not effective in treating certain types of pain, the most notable example being "neuropathic pain", a type of pain experienced when a patient's nervous system is suffering from some type of pathological damage or condition (hence the term "neuro-pathic"). There are several different types of neuropathic pain, but a common denominator of all types is that they do not respond adequately to opiate medications; this trait is so prevalent that physicians tend to view "neuropathic pain" as being synonymous with pain that does not respond adequately to opiates. When a pain condition in a specific patient will not respond adequately to opiates, it is assumed that: (i) the patient is suffering from neuropathic pain; and, (ii) the neuronal pathways that are causing or aggravating the pain condition in that patient are not pathways that use opiate receptors; rather, they convey pain messages via other neurotransmitter/receptor systems.

Most cases of neuropathic pain appear to involve chronic conditions that arise when nerve fibers or endings in a certain part of the body (or the larger neuronal networks they are connected to, which may include neurons located in the spinal cord) have become hyper-sensitive (also referred to as being hyper-irritable, or being in a "kindled" or "wind-up" condition). In this condition, certain neuronal endings, receptors, or other components

or circuits are in a chronic state of abnormally high sensitivity, and/or have abnormally low triggering thresholds. In this state, they convey (either spontaneously, or in response to very mild stimuli that would not be painful to a healthy person) far too many nerve signals of the type classified by neurologists as "nociceptive" nerve impulses (i.e., nerve impulses interpreted by the nervous system as signalling pain; this class of signals is distinct from other types of nerve impulses, such as sensory signals for light, smell, taste, etc.).

A person with a hypersensitized or "kindled" neuropathic condition is comparable to a person whose eyes were dilated by a drug, during an eye exam, and who is then forced to look directly into a bright light. Just as bright light is very unpleasant and even painful to a person with dilated eyes, a patient subject to neuropathic pain will suffer pain, even when no stimulus has been inflicted that would be perceived as painful by a person who is not suffering from the neuropathic hypersensitivity.

Examples of neuropathic pain include: (i) chronic painful states that occur in association with diabetes, often referred to as "diabetic neuropathy"; (ii) chronic pain associated with traumatic injury to the peripheral nervous system; (iii) chronic pain resulting from herpes zoster (also known as shingles, or post-herpetic neuropathy) or similar infections that attack and damage nerve fibers or endings; (iv) post-operative pain, which arises after surgery and then lingers far beyond a normal convalescent period; (v) "phantom limb" pain, in which an amputee suffers from feelings of pain or discomfort that seems to originate in the missing limb; and (vi) causalgia, which refers to pain that is perceived as a burning sensation ("causalgia" comes from the same Greek root as "cautery", and has nothing to do with causation).

In addition, certain patterns of neuropathic pain commonly arise in certain parts of the central or peripheral nervous system. Examples include trigeminal pain, which afflicts the trigeminal nerve in the facial region, and arachnoiditis, in which a certain layer of membrane that generally surrounds the brain and spinal cord becomes damaged and/or inflamed, usually due to trauma, surgery, or infection.

All of these conditions appear to share at least some underlying mechanisms and/or traits. In particular, they share the common distinction that they all involve chronic pain, and the pain reaches a level regarded by the patient and the treating physician as "intractable". As used herein, the term intractable implies that: (i) a pain condition cannot be adequately relieved by opiates or other currently available pain medications; and (ii) any short-term relief provided by opiates or other drugs is usually accompanied by serious side

effects, such as sedation, gastrointestinal disorders, etc.

Any references herein to relief, short-term relief, or similar terms, refer to an effective form of non-sedating relief. Obviously, if a patient is rendered unconscious by a powerful sedative, the patient will feel no pain for as long as he or she remains unconscious. However, just as obviously, that is not the goal of an effective treatment for chronic pain.

In this context, terms such as sedative, sedating, or sedation do not imply a treatment that is soothing, relaxing, and appreciated; instead, if a drug must be used on a chronic, daily basis for months or years, "sedating" indicates a highly undesired and often debilitating interference with mental clarity, and should be regarded in the same general category as "addictive narcotic". One of the most troubling and depressing side effects of pain-killing drugs, in the view of anyone who must take them to treat chronic intractable pain, is the severe disruption they impose on a patient's mental clarity. Sedating pain-killers make it tiring and difficult, and often impossible, for a patient to have the sort of normal, healthy, happy activities and relationships that he or she enjoyed before the chronic pain began. Sedation also substantially increases the risk of serious accidents, such as a collision while driving, or a fall while walking (which poses a serious risk of a broken hip, leg, or arm, especially in elderly patients).

If an effective *and non-sedating* treatment for neuropathic or other chronic or intractable pain could be discovered and made publicly available, it would be a major advance over opiates and other currently available drug treatments, and it would offer blessed relief to literally millions of people around the world.

This invention discloses what appears to be a major advance in that direction. To understand how this drug treatment works, and which drugs are covered by certain terms used in the text and claims below, additional background information needs to be provided on certain types of "receptor" systems that are present on the surfaces of neurons.

NEUROTRANSMITTER SYSTEMS

Several systems, involving neurotransmitter molecules and the neuronal receptors they interact with, are involved in transmitting nerve signals (including pain signals) from one neuron to another.

An introduction to the structure and functioning of neuronal receptors and neurotransmitters can be found in textbooks such as *Principles of Neuroscience* (E.R.

Kandel et al, editors, 4th ed., McGraw Hill, 2000). Very briefly, "neurotransmitter receptors" are specialized membrane sites that are exposed and accessible on certain surface areas of neurons, in the "synaptic" junctions between neurons. Transmission of a nerve impulse (also called a signal, message, depolarizing event, etc.) from one neuron to another, through a synaptic junction, is achieved by the release of neurotransmitter molecules (such as glutamate or acetylcholine, two of the most important neurotransmitters) by the transmitting neuron, into the liquid that fills the gap in a synaptic junction with the signal-receiving neuron. The neurotransmitter molecule briefly binds to an exposed and accessible portion of a receptor protein, which straddles the neuronal membrane. This binding reaction between the transmitter molecule and the receptor protein triggers a cellular reaction (such as opening an ion channel, in glutamate receptors).

With a few exceptions, each type of neuronal receptor is triggered by only one type of neurotransmitter. Therefore, each of the various classes of transmitter-and-receptor pairings in the central nervous system (CNS) can be regarded as a "system". The CNS has a glutamate system, an acetylcholine system (usually called the cholinergic system), a dopamine system, a serotonin system, an adrenergic system, and a variety of other similar systems using other specific neurotransmitters.

In addition, most receptor systems have multiple subclasses. For example, the glutamate receptor system is subdivided into three major subclasses, designated as the NMDA, kainate, and AMPA subclasses. In the brain, all three subclasses are triggered by glutamate (and by aspartate, to a much lesser extent). However, in cell culture tests, scientists have identified "probe drugs" which can selectively activate one particular subclass of glutamate receptors. A probe drug called N-methyl-D-aspartate (abbreviated as NMDA), which does not exist inside the brain, powerfully triggers a certain class of glutamate receptors, but has little or no effect on the other two subclasses. Accordingly, those glutamate receptors that are activated by NMDA are called NMDA receptors.

In a similar manner, acetylchcoline (ACh) receptors are subdivided into the "muscarinic" and "nicotinic" classes, and those classes are divided into still more subclasses; for example, muscarinic ACh receptors are subdivided into m1, m2, m3, m4, and m5 subclasses.

Another transmitter-receptor system that is important to this invention is the "adrenergic" system. Since it is directly relevant to this invention, it is discussed in some detail below.

The glutamate and acetylcholine (ACh) systems are both excitatory, since the action of glutamate or ACh at those receptors normally results in a neuronal firing event (unless that receptor or neuron has been inhibited by one of the inhibitory neurotransmitter systems). Various other transmitter-receptor pairings are regarded as inhibitory systems. When an inhibitory neurotransmitter reacts with an inhibitory receptor, rather than triggering a neuronal firing event in a manner comparable to glutamate or ACh, the inhibitory reaction causes the neuron to become less susceptible to excitation, even if its synaptic receptors are contacted by glutamate or ACh. The dopamine, serotonin, and GABA systems are all regarded as inhibitory.

For the most part, the adrenergic system is regarded as an inhibitory system, rather than an excitatory system. The adrenergic system is quite complicated, and acts in various different ways, both inside the CNS, and outside the CNS. Inside the CNS, it is regarded as predominantly inhibitory.

Inhibitory systems play a crucial role in the proper functioning of the CNS. By way of analogy, they are similar to a tuning system which allows a television set to process electromagnetic waves that contain dozens or even hundreds of channels, and present a single coherent picture on the screen, with accompanying sound. In a similar manner, inhibitory neurotransmitters allow the CNS to process huge numbers of input signals in ways that generate coherent thoughts, useful muscle and organ control, etc.

Another pair of terms relevant to this invention also needs to be established. As used herein, a receptor "agonist" is a molecule which increases activity levels at that type of receptor. By contrast, a receptor "antagonist" is a molecule which reduces activation of a receptor type by its normal neurotransmitter.

Many agonists exert their effects by binding directly to the receptor, in a manner which "triggers" the receptor. However, other types of agonists (as that term is used herein) use alternate methods, such as increasing the concentration of the natural transmitter molecule in the extra-cellular fluid surrounding the neuronal receptors. Examples include cholinesterase inhibitor drugs, which prevent ACh molecules from being degraded rapidly by cholinesterase enzymes, and "serotonin uptake inhibitors", which slow down the rate at which serotonin is pumped back into neurons after it has been released. Not all agonists are excitatory; for example, a GABA agonist will inhibit neuronal firings, since that is the same function exerted in the CNS by GABA.

All references herein to agonists or antagonists (or to drugs of any sort) refer to

"exogenous" compounds, i.e., compounds (other than foods) that are synthesized outside an animal or human, and then administered to the animal or human. As used herein, terms such as agonist, antagonist, or drug exclude naturally occurring neurotransmitters that are found under normal conditions inside the CNS of an animal or person. The term "compound" is used broadly herein; in addition to drugs, it includes newly-synthesized molecules that are of interest for possible medical use. If a compound passes various initial hurdles and is actually tested in animals, and is shown in such tests to be pharmaceutically acceptable, it is thereafter referred to as a drug.

Much of neurology and neuropharmacology focus on "exogenous" (non-natural) drugs that mimic the action of neurotransmitters at certain classes (or subclasses) of neuronal receptors. Research on neuronal receptor systems is often performed using agonist drugs that activate one or more classes of neuronal receptors, and/or antagonist drugs that prevent or reduce activation of one or more classes of neuronal receptors. This has been rendered possible and even routine by means of various research instruments, including very small electrodes that can detect a single firing event by a single neuron, either *in vitro* (using cell culture tests), or *in vivo* (using lab animals, or even human subjects during a neurosurgical operation).

Accordingly, neuroactive drugs are commonly described by reference to their interactions with a class of neuronal receptors. As one example, MK-801, phencyclidine, ketamine, and tiletamine are all immediately recognized among neurologists as NMDA antagonist drugs, even though their chemical structures are substantially different from each other, since they all bind to a certain receptor site associated with the NMDA receptor complex.

GLUTAMATE AND NMDA RECEPTORS; NMDA ANTAGONIST DRUGS

Glutamate (the ionized form of glutamic acid, an amino acid) is a major excitatory neurotransmitter. Unlike molecules of acetylcholine, which are rapidly broken apart by enzymes after they are released by a synaptic receptor, glutamate molecules that have been released by a synaptic receptor must be pumped back inside a neuron or glial cell.

The glutamate pumping mechanism requires energy to drive it. Therefore, if a region of the brain or spinal cord begins to suffer from an ischemic (inadequate blood flow) or hypoxic (inadequate oxygen supply) crisis, due to a stroke, cardiac arrest, head trauma, etc., excess free glutamate molecules can begin to accumulate in that portion of the brain.

Because of certain ways that stressed neurons and glial cells respond to that type of crisis, this can lead to a type of over-excitation that can permanently damage or even kill neurons. This phenomenon, known as "excitotoxicity", can severely worsen the extent and severity of brain damage that occurs in the hours and days after a stroke, head trauma, cardiac arrest, severe epileptic seizure, or similar crisis.

By the early 1980s, it was becoming established (published studies are reviewed in Olney 1990 and Choi 1992) that excessive activation of NMDA receptors will aggravate and increase the brain damage caused by a stroke, head trauma, or similar crisis. In response, a number of pharmaceutical companies began developing NMDA antagonist drugs (i.e., drugs which suppress glutamate-induced neuronal firings by blocking the NMDA receptor complex) as neuroprotective (anti-excitotoxic) agents.

By the mid-1980's, a number of candidate NMDA antagonists were becoming available to neurology researchers. As soon as these drugs became available, neurologists (who were well aware by then of the highly important role of NMDA receptors in CNS functioning) began testing these compounds, to evaluate their effects on nearly every conceivable type of neurological functioning, ranging from pain, to sensory processing, to memory. By the mid to late 1980s, a number of researchers had reported that NMDA antagonist drugs can relieve neuropathic pain (e.g., Raigorodsky et al 1987; Aaronsen et al 1987; Woolf et al 1989; Davar et al 1991; Seltzer et al 1991; Yamamoto et al 1992; Mao et al 1992; Kristensen et al 1992; Backonja et al 1994).

However, by the late 1980's, neurologists were also realizing that NMDA antagonist drugs can cause serious side effects, including psychotic reactions and physical injury to neurons, when administered at the dosages required to relieve neuropathic pain, or to prevent excitotoxic neuronal damage after a stroke or other acute insult.

In humans, it is well documented that NMDA antagonist drugs cause psychotic side effects, including hallucinations and delusions. People who abuse phencyclidine (also known as PCP, or "angel dust") often suffer acute psychotic episodes, and surgical patients emerging from ketamine anesthesia often suffer "emergence" psychoses unless they are also treated with a second drug to suppress that reaction. Both phencyclidine and ketamine are NMDA antagonists.

In experimental animals, analysis of brain tissue following treatment with an NMDA antagonist drug reveals that NMDA antagonists cause acute physical injury to neurons which, in extreme cases, can lead to neuronal death and permanent brain damage. These

neurotoxic effects occur in several specific regions of the brain, including two regions known as the posterior cingulate and retrosplenial (PC/RS) cortex, as well as the hippocampus. These brain regions receive input from a variety of other brain regions, and they perform important "central processing" functions (which can also be regarded as "switchboard" or "clearinghouse" functions).

The damage that occurs in the most vulnerable portions of the brain is manifested, at a fairly early stage, by the formation of empty "vacuoles" inside the affected neurons. These vacuoles, which do not occur in healthy neurons, provide a useful and convenient way to measure and quantify the damage to vulnerable neurons, since the vacuoles can be easily seen and counted, using microscopic examination of tissue slices. Other types of neuronal damage can also be detected if various analytical steps are taken; as one example, affected neurons begin expressing "heat shock" proteins, which indicate that the neurons containing those proteins are being subjected to severe and potentially lethal stress. In addition, potent NMDA antagonists at substantial dosages can cause neuronal death, which can be measured using various types of stains that cannot permeate into viable neurons. Neuronal vacuoles, heat shock protein expression, mitochondrial damage, and other neurotoxic manifestations are discussed in more detail in items such as US 5,877,173 (Olney et al 1999).

There is considerable evidence indicating that these same regions of the brain are also involved in causing psychotic effects, in humans. Evidence that the same neural networks are involved in both the psychotic and neurotoxic changes strongly suggests that humans who take NMDA antagonist drugs, in addition to suffering transient effects such as hallucinations, are at a serious risk of the same type of physical injury to neurons that can be shown to occur in test animals.

Because NMDA antagonist drugs are known to cause psychoto-mimetic effects in humans, and are strongly suspected of posing serious and unacceptable risks of permanent brain damage, efforts to develop NMDA antagonist drugs for neuroprotective purposes following a stroke or similar crisis, or for use in treating neuropathic pain or other chronic pain, have uniformly failed. Even though at least a dozen major drug companies launched major research programs, attempting to develop effective yet safe NMDA antagonists, every such effort has failed. As this is being written, in March 2001 (nearly 20 years after the first known NMDA antagonist drugs were announced), not a single known NMDA antagonist drug has ever been approved for public sale and use, by the U.S. Food and Drug

Administration.

The only publicly available drugs that are known to have some degree of NMDA antagonist activity fall into two categories. The first category includes two surgical anesthetics, ketamine and tiletamine, and these were approved by the FDA many years before their role as NMDA antagonists were known. The second category includes a few drugs (such as dextromethorphan and procyclidine) which have strong primary activities involving completely different neuronal receptor systems, and which were discovered, after many years of public use, to have relatively mild and weak secondary activities as NMDA antagonists.

The failure of any drug company to successfully launch any known NMDA antagonist drug as a commercial product is also noteworthy, and perhaps even peculiar, because it has been known for nearly 10 years that any of several types of drugs can effectively block the neurotoxic side effects of NMDA antagonists, in test animals. When used for this purpose, these drugs are referred to herein as "safener" drugs, borrowing a term that is well known in other chemical industries, such as the herbicide industry. Administration of one or more of these "safener" drugs can effectively block the neurotoxic side effects caused by NMDA antagonists, in test animals.

These types of "safener" drugs can be divided into several categories, depending on which neurotransmitter system they affect. Briefly, they include: (1) anticholinergic drugs, such as scopolamine, as described in Olney et al 1991 and US patent 5,034,400 (Olney 1991); (2) GABA agonist drugs, as described in US patent 5,474,990 (Olney 1995); (3) alpha-2 ($\alpha 2$) adrenergic agonists, discussed in detail below; and, (4) drugs that suppress activity at kainate and AMPA receptors, as described in US patent 5,767,130 (Olney 1998).

Despite all these options (and several others, not mentioned above), most of which involve well-known and long-accepted drugs, and despite the demonstration in test animals that the neurotoxic side effects of potent NMDA antagonists can be greatly reduced or entirely eliminated by these types of "safener" drugs, the pharmaceutical industry has steered entirely away from any effort to develop and commercialize any drug combination involving an NMDA antagonist drug, accompanied by a second drug that would prevent the neurotoxic side effects of the NMDA antagonist drug. Instead, efforts have continued to focus on a search for an NMDA antagonist drug that would not cause neurotoxic side effects, at the dosages needed to exert a beneficial neuroprotective effect.

Because of the prominent role one of the inventors herein (Olney) played, first in

elucidating the neurotoxic effects caused by excessive quantities of glutamate (Olney 1969), then in clearly locating and identifying the types of measurable neuronal damage that were being inflicted by NMDA antagonist drugs in the brains of lab animals (Olney et al 1989), Olney's laboratories were frequently requested to evaluate the neurotoxic risks of new candidate drugs that were becoming the heavily-investigated "lead compounds" in the drug companies' efforts to find a safe NMDA antagonist.

However, in every such investigation, Olney's tests disclosed that, if an NMDA antagonist drug was used in a quantity sufficient to actually reduce excitotoxic brain damage following a stroke or other brain insult, then it also caused neurotoxic vacuoles. Olney's research repeatedly revealed that even weak NMDA antagonists (such as dextromethorphan, the well-known cough suppressant that has been used for decades in cough syrups) would begin causing neurotoxic effects, if administered at dosages sufficient to reduce excitotoxic brain damage following a hypoxic crisis.

In the final analysis, the problem was not that the drugs were too potent to be used safely; instead, the problem was in certain inherent and unavoidable traits of the neuronal circuitry inside the brain. Glutamate molecules and NMDA receptors are so heavily and deeply involved, in so many crucially important circuits and regions inside the brain, that if any NMDA blocker drug is administered at a dosage which is potent enough to substantially slow down the excitotoxic processes triggered by excess glutamate accumulation inside a brain region suffering from a hypoxic crisis such as a stroke or cardiac arrest, then that protective dosage of that NMDA blocker drug will also be potent enough to trigger major disruptions and derangements in other crucially important neuronal circuits, as well.

In other words, because of the ubiquity of the NMDA receptor system inside the brain, any drug which blocks NMDA receptors at levels that can help suppress excitotoxic cell death, after a brain crisis, will also trigger major disruptions and derangements in other neuronal circuits. These disruptions and derangements were of such a type and magnitude that they inevitably led to toxic damage, affecting specific neurons in the cerebral cortex which perform important "clearinghouse" or "switchboard" functions.

In view of those consistent and repeated results from dozens of different drug tests on animals, Olney concluded that by far the best way, and probably the only realistic way, to reduce and prevent the neurotoxic side effects of NMDA antagonists was not by developing better NMDA antagonists, but by instead developing ways of coadministering NMDA antagonists along with other classes of drugs, which were eventually termed

"safener" drugs, borrowing an old chemical term that had previously been used in the herbicide industry.

The first drugs that were discovered to block the toxic side effects of NMDA antagonist drugs were drugs that suppress activity at muscarinic receptors, which are a subclass of receptors activated by acetylcholine (ACh). These drugs, called "anti-cholinergic" or "anti-muscarinic" drugs, are discussed in the next section.

THE CHOLINERGIC SYSTEM; ANTI-MUSCARINIC DRUGS

The "cholinergic" system, which uses acetylcholine (ACh) as its neurotransmitter, is another highly important excitatory system; the glutamate and cholinergic systems are the two most prevalent and important excitatory systems in any mammalian nervous system. Reviews of the physiology and activities of the cholinergic system include Aprison et al 1996, Zimmermann et al 1996, Everitt et al 1997, Buerkle et al 1997, Weinstock 1997, Kubo 1998, Israel et al 1998, and Oda 2000. Reviews of drugs used to modify activity at cholinergic receptors include Sullivan et al 1995, Iversen 1997, Geroldi et al 1997, Patocka 1998, and Tune et al 1998.

The two major classes of cholinergic receptors are called muscarinic, and nicotinic. Muscarinic receptors are relevant to this invention, and they have been further subdivided into classes designated as m1, m2, m3, m4 and m5 receptors. Drugs that suppress activity at one or more types of muscarinic receptors are well-known, and have played significant roles in medicine for decades.

Drugs that suppress activity at cholinergic receptors are often called anti-cholinergic drugs, which means the same thing as "cholinergic antagonists." Similarly, drugs that suppress activity at muscarinic receptors are referred to herein as anti-muscarinic drugs. The term, "*selective* anti-muscarinic drug," refers to an anti-cholinergic drug with substantially greater affinity for one or more types of muscarine receptors than for nicotine receptors.

A specific class of selective anti-muscarinic drugs have molecular structures that are referred to as aryl-cyclo-alkanol-amines (referred to by the acronym, "ACAA" drugs). As indicated by that name, these drugs have an aryl (benzene or similar) ring, and a non-aromatic ring (such as cyclo-hexane), coupled to a short-chain alkyl group which has a pendant hydroxy group (i.e., an alkyl-alcohol, or alkanol). The alkanol component is also bonded to an amine structure (which is a heterocyclic ring in some but not all ACAA

compounds).

The chemical structures of all compounds listed herein are illustrated in various reference works, including The Merck Index, various editions of Goodman and Gilman, eds., *The Pharmacological Basis of Therapeutics*, and numerous review articles, including those cited above.

ACAA drugs such as procyclidine and biperiden were used for decades as anti-cholinergic agents, for two main purposes: (i) to treat patients suffering from Parkinson's disease; and, (ii) to treat patients who began suffering from Parkinson-like symptoms (such as muscular rigidity) as side effects of some of the earlier classes of anti-psychotic drugs that were used in the 1960's and 1970's (see AMA Drug Evaluations, 1971).

In recent years, these ACAA drugs have fallen into relative disuse, for two reasons. First, newer and better drugs have been developed for treating Parkinson's disease. And second, improved antipsychotic drugs have become available which do not cause the Parkinson-like side effects caused by earlier generations of antipsychotic drugs; therefore, anti-cholinergic drugs such as the ACAA drugs are no longer needed to control Parkinson-like side effects of other drugs.

Accordingly, ACAA drugs no longer receive the attention they received in earlier editions of Goodman and Gilman (the most widely used reference work of its kind). Most of the ACAA drugs named herein are shown, with their complete structures, in the fifth edition (1975) of Goodman and Gilman, but they are no longer shown in any recent editions. Examples of such older ACAA drugs that are no longer discussed in any detail in Goodman and Gilman include glycopyrrolate (ROBINUL), hexocylium (TRAL), oxyphenonium (ANTRENYL), tridihexethyl (PATHILON), and oxyphencyclomine (DARICON).

In addition to various drugs which fall squarely within the aryl-cyclo-alkanol-amine category, various other drugs with known anti-muscarinic activity have similar chemical structures, but do not fall squarely within the definition of "aryl-cyclo-alkanol-amines". Examples include mepenzolate (sold under the trademark CANTIL), piperodolate (DACTIL), isopropamide (DARBID), thiphenamil (TROCINATE), adiphenine (TRASENTINE), dicyclomine (BENTYL), and poldine (NACTON). The structures of several such compounds are shown in sources such as the Merck Index, older editions of Goodman and Gilman, etc. Drugs such as these are referred to herein as "ACAA analogs". They are discussed in more detail below, under the subheading "Analogs and Derivatives."

All references below to ACAA drugs as a class are deemed to also refer to related analogs and derivatives of ACAA drugs, but only to analogs and derivatives which have certain essential properties which make them of interest herein for use in pain relief.

Several historical developments also deserve attention in any analysis of ACAA compounds which may be useful as pain-relieving drugs. As briefly mentioned above, about 10 years ago, one of the Applicants herein (Olney) discovered that a number of well-known anti-cholinergic drugs (including but not limited to some ACAA drugs, such as procyclidine and biperiden) have a property that should have been of considerable interest to a number of companies and researchers that were actively trying to find ways to safely manipulate and modify activity at NMDA receptors. These anti-cholinergic drugs, if coadministered together with a potent NMDA antagonist that has severe neurotoxic side effects, will prevent the toxic side effects of the NMDA antagonist. That discovery (published in Olney et al 1991, and in US 5,034,400, Olney 1991) was the first discovery and demonstration of a "safener" agent that could reduce and even eliminate the neurotoxic side effects of potent NMDA antagonists.

However, those 1991 reports were puzzling and apparently paradoxical, when viewed in light of an earlier published report. Several years earlier, in Olney et al 1987, the same research team had reported that several anti-cholinergic ACAA drugs also have significant NMDA antagonist activity.

The paradox was this: if an ACAA drug has NMDA antagonist activity, and if it is administered together with another drug that has even stronger NMDA antagonist activity, a logical person who understands the neurotoxic side effects of NMDA antagonist drugs would expect that the combined effect of administering two NMDA antagonist drugs, together, would be to increase (i.e., aggravate and worsen) the toxic side effects that NMDA antagonist drugs are known to cause. However, the research results clearly showed the opposite: all signs of the neurotoxic side effects of the potent NMDA blocking drug were abolished, when an ACAA drug having both anti-cholinergic and NMDA antagonist activity was administered together with the potent NMDA blocking drug.

When this latter finding was published (Olney et al 1991), other researchers working in this field considered it contradictory and did not know how to interpret it. It appeared that either Olney's initial claim, in 1987, that ACAA drugs have NMDA antagonist effects must be wrong, or his subsequent claim, in 1991, that ACAA drugs counteract NMDA antagonist effects, must be wrong. Thus, both sets of results were treated with skepticism,

which is not uncommon in the world of science when a finding that appears to contradict conventional wisdom has been published by only one research team.

The attitude of skepticism referred to above is evidenced by the fact that, in the many years since the Olney et al 1987 report, there have been no publications from any other laboratories reporting any effort to confirm, deny, or further explore any of the implications of those findings. This is a curious and powerful commentary, when viewed in light of the two facts: (1) during the last two decades, drug companies have spent hundreds of millions of dollars, trying to find or develop drugs that can block NMDA receptors without causing neurotoxic side effects; and, (2) it is widely recognized and generally agreed that if non-toxic NMDA blockers could be created or discovered, they would have tremendous potential for treating a wide range of neurological conditions, including stroke, epilepsy, head trauma and neuropathic pain.

Nevertheless, despite the implication of the findings reported in Olney et al 1987, neither academic nor industry researchers attempted to confirm, deny, or even explore the possibility that ACAA drugs might be able to block NMDA receptors. To the best of the Inventors' knowledge and belief, no studies have ever been reported in which ACAA drugs were tested for efficacy in treating any neurological disorder in which excitotoxic brain damage might be involved (such as stroke, cardiac arrest, head trauma, etc.), or in which ACAA drugs were tested for efficacy in treating neuropathic pain, or any other chronic pain condition.

Skepticism regarding whether ACAA drugs are NMDA antagonists, and whether ACAA drugs can relieve neuropathic pain, has also been powerfully fueled and supported by two other factors.

The first factor is this: many laboratories have reported that NMDA antagonists are indeed effective in relieving neuropathic pain, in tests using lab animals (e.g., Davar et al 1991) and humans (e.g., Kristensen et al 1992). Based on those actual test results, and based on the growing understanding of the roles that NMDA receptors play in neuropathic pain, there is a generally shared assumption that, if a safe NMDA antagonist drug were available to the public, it likely would be very useful, indeed, in relieving at least some types of neuropathic pain, or other chronic pain. The problem is not based on any concern that NMDA antagonists would not be effective in relieving pain; the problem, instead, is that the ones that have been shown to work effectively have unacceptably toxic side effects.

That factor must be placed directly alongside the second factor: millions of people

have been treated with ACAA drugs, over a span of decades. Many of those people (including many elderly patients) suffered from a wide range of ailments, some of which were painful. And yet, to the best of the Inventors' knowldege and belief, no evidence (not even anecdotal evidence) has ever been published, indicating that ACAA drugs could provide any relief from neuropathic pain, or any other kind of pain.

If ACAA drugs do indeed have a substantial level of NMDA antagonist activity, one would assume that their ability to reduce pain, based on that NMDA antagonist activity, would have been noticed by someone, at some time, during the decades that these drugs were in widespread use.

It is clear, therefore, that Olney's assertions pertaining to the NMDA antagonist properties of ACAA drugs have been ignored or disbelieved, by those schooled in the field of neurological research, and by companies and researchers that are actively pursuing efforts to develop NMDA antagonist drugs.

In addition, as described in the following paragraphs, another well-known line of prior art teaches directly away from this invention, and prevented those skilled in the art from suspecting that ACAA drugs would be effective in relieving neuropathic pain.

PRIOR ART: MUSCARINIC AGONISTS AS PAIN RELIEVERS

Another line of prior art directly contradicts and teaches away from the current invention. A substantial number of prior art articles, authored by numerous researchers over a span of 50 years, teach that muscarinic *agonists* have substantial pain-relieving activity. That is crucially important, because muscarinic *agonists* are drugs that stimulate, rather than suppress, neurotransmission via muscarinic cholinergic receptors. Clearly, that activity is the exact opposite of the activity caused by muscarinic *antagonists* (suppressors), such as the ACAA drugs involved in this invention.

The relevant reports are reviewed in Poyhia 2000. Briefly, Flodmark et al 1945 reported, more than 50 years ago, that a drug called prostigmine has pain-relieving activity. Prostigmine is a "cholinesterase inhibitor", i.e., it slows down cholinesterase enzymes, which otherwise will rapidly break apart ACh molecules after they are released from ACh receptors. By preventing cholinesterase enzymes from quickly degrading ACh molecules, prostigmine increases the quantity of ACh that is present in the extra-cellular fluids which bathe cholinergic receptors.

This increase in ACh concentrations leads directly to an increase in ACh receptor

activity. Accordingly, prostigmine is a cholinergic agonist; it has the opposite effect of a cholinergic antagonist, such as procyclidine. And yet, it was reported to be a pain-relieving drug.

That report was largely ignored for some years. Then, interest in the medical effects of tobacco and cigarettes (which contain nicotine, which triggers the nicotine class of cholinergic receptors) began provoking more research into the neurological and medical effects of cholinergic agonists. That led to a second round of reports which described the pain-relieving properties of cholinergic agonists (Mattila et al 1968; Bannon et al 1971).

Cholinesterase inhibitors, which increase the concentrations of ACh in extracellular fluids, are completely non-specific; they cannot selectively activate only certain subclasses of cholinergic receptors, while leaving other subclasses alone. Therefore, if tested in dosages that were high enough to provide substantial pain relief, they had two important shortcomings: (i) they caused intolerable levels of unwanted side effects, and (ii) their duration of pain relief was short, and wore off quickly. So, they did not merit or establish serious or widespread use as pain-controlling drugs, in the human clinic.

However, as more years passed, three other developments eventually led back to cholinergic agonists as pain-relieving drugs. The first development was the creation of receptor-specific selective agonists, which could target and activate only certain subtypes of cholinergic receptors, without activating or bothering other subtypes. As a general rule, the problem of unwanted side effects will usually decrease, and lower doses of a compound of interest can be used, if a more highly selective agent can be used, which does not manipulate and alter as many different types of neuronal receptors as a non-selective drug.

The second development was the expanding use of "intrathecal" injections (i.e., injection of drugs directly into the spinal fluid that is contained by the dural and arachnoid membranes that surround the spinal cord) and "epidural" injections (i.e., injection of drugs into the space adjacent to the dural membrane). To some extent, expanded use of spinal anesthesia was being driven and promoted by its increasing use in women who were delivering babies. It was widely recognized that one of the primary benefits of spinal injections, in women in the throes of labor, was that the drug did not enter the mother's circulating blood in a substantial quantity, and therefore posed no risk of affecting the vital functions of the baby that was being born.

The third development grew out of the expanding attention that was being given to pain management in terminally ill patients, especially cancer patients. As improvements in

chemotherapy began keeping gravely ill cancer patients alive longer and longer, it became more important for pain management specialists to be able to treat such patients for prolonged periods.

As those factors converged, more anesthesiologists began administering more anesthetics via intrathecal or epidural routes. As they did, they realized that a number of old anesthetic drugs, which had caused too many undesired side effects or which had disappeared too quickly when administered using the old modes of administration, might deserve to be reevaluated using intrathecal administration, since a drug injected directly into the spinal region remained largely restricted to that region, and would not pose substantial risks of adverse symptoms.

Accordingly, anesthesiologists began using intrathecal and epidural injections to re-evaluate the same types of cholinesterase inhibitors that had caused too many side effects when administered systemically back in the 1960's. This led to articles such as Collins 1995, entitled, "Spinally administered neostigmine -- something to celebrate," in the journal *Anesthesiology*.

More than a dozen other articles, reporting similar results, were published during 1995-2000; as noted above, they are cited and summarized in Poyhia et al 2000, a short review article that is titled, "Cholinergic mechanisms of analgesia."

The crucial point that must be recognized about all of those articles and all of the research they describe is this: they all report the successful and effective use of cholinergic *agonists* (i.e., cholinergic receptor *stimulants*), for treating pain.

By contrast, this invention teaches the exact opposite. This invention teaches that cholinergic antagonists (i.e., cholinergic receptor blockers) can be used safely and effectively for treating pain -- but only if combined with a second drug that has a completely different activity, at a completely different set of neuronal receptors. Clearly, this current invention teaches in the exact opposite direction from the fairly extensive and accumulated prior art that is cited and summarized in Poyhia 2000.

TRI-CYCLIC ANTI-MUSCARINIC DRUGS

Another important class of drugs which are used for various purposes (mainly as anti-depressants, or as anti-psychotics) are also known to have anti-muscarinic activity, as a side effect. These molecules have chemical structures referred to herein as tri-cyclo-alkyl-amines (abbreviated herein as TCAA's). As indicated by that name, each of these drugs has

a tricyclic structure, having three rings bonded to each other in a linear manner. An additional structure, having an alkyl component and at least one nitrogen atom, is bonded to the tricyclic component.

One important subclass of the TCAA group uses phenothiazine as its tricyclic structure. Phenothiazine has a nitrogen atom and a sulfur atom, in a center ring located between two benzene groups; accordingly, it can be regarded as having a sulfur atom and a nitrogen atom, holding two benzene rings together. One example is ethopropazine (sold under the trademark PARSIDOL). Most phenothiazine compounds are used as anti-psychotics; ethopropazine is an exception. It has been used for decades as an anti-cholinergic agent, for two main purposes: (i) to treat patients suffering from Parkinson's disease; and, (ii) to treat patients who began suffering from Parkinson-like symptoms (such as muscular rigidity) as side effects of some of the earlier classes of anti-psychotic drugs that were used in the 1960's and 1970's (see AMA Drug Evaluations, 1971).

However, in recent years, anti-cholinergic TCAA drugs such as ethopropazine have fallen into relative disuse, for two reasons. First, newer and better drugs have been developed for treating Parkinson's disease. And second, improved antipsychotic drugs became available which did not cause the Parkinson-like side effects caused by earlier generations of antipsychotic drugs.

Returning to the subclass of tricyclic drugs which contain phenothiazine as their tricyclic structure, ethopropazine does not have a strongly electronegative (electron-withdrawing) group at the #2 position. Most other phenothiazine drugs that have been developed commercially have chlorine or other strongly negative groups at their #2 positions. This increases their potency as neuroactive agents, and these compounds were used mainly as anti-psychotic drugs when they were popular, mainly during the 1960's through 1980's. Examples of phenothiazine compounds used as anti-psychotic drugs include chlorpromazine (sold under the trademark THORAZINE), trifluprомazine (VESPRIN), mesoridazine (SERENTIL), thioridazine (MELLARIL), acetophenazine (TINDAL), fluphenazine (PROLIXIN), perphenazine (TRILAFON), trifluoperazine (SUPRAZINE), and dixyrazine (ESOCALM). Their structures are shown in various references, such as the Merck Index, various review articles, and older editions of Goodman and Gilman. It is generally believed that their anti-psychotic activity was mainly due to their activity in blocking dopamine receptors; however, that activity caused Parkinson-like symptoms as a side effect, which led to the use of anti-cholinergic drugs (including ethopropazine) to help

reduce and control the Parkinson-like symptoms.

Various other TCAA compounds that have been commercialized have six-member center rings other than phenothiazine. Several tricyclic anti-psychotics used thioxanthene structures, with a sulfur atom but no nitrogen atom in a six-member center ring; examples include chlorprothixene, clopenthixol, flupentixal, piflutixol, and thiothixene.

Still other TCAA compounds with six-member center rings used a xanthene structure, with a single oxygen atom as the "hetero" atom in the center ring; however, most of these compounds were not used as anti-psychotic agents. Examples include methantheline (BANTHINE) and propantheline (PRO-BANTHENE), both of which were used as anti-cholinergics, and maprotiline (DEPRILEPT), used as an anti-depressant.

Since all of the TCAA compounds mentioned above (including the phenothiazine compounds) have six-member center rings flanked by two benzene rings, these compounds can be regarded as having "dibenzo-cyclohexyl" structures.

Another important class of neuroactive TCAA compounds has seven-member center rings, flanked by two benzene rings. This chemical structure can be called a "dibenzo-cycloheptene". Although a few of these compounds (such as loxapine) have been used as anti-psychotic agents, most commercial tricyclic drugs with seven-member center rings are used as anti-depressants. One of the oldest and best-known agents in this class is amitryptilene, which has been used as an anti-depressant for decades, under various trademarks such as ELAVIL.

Other tricyclic anti-depressants with seven-member center rings include imipramine (DEPRINOL, IMIDOL, etc.), trimipramine (SURMONTIL), doxepin (CURATIN), desipramine (NORTIMIL; also referred to by the chemical name desmethylimipramine), nortriptyline (ALLEGRIN, NORZEPINE, etc.), protriptyline (TRIPTIL), amoxapine (MOXADIL), and clomipramine (ANAFRANIL; also referred to by the chemical name chlorimipramine). Compounds with tricyclic structures are used so widely as anti-depressants that they have acquired a general category name, "tricyclic anti-depressants".

Nearly all TCAA compounds that have been commercialized have some degree of anti-muscarinic activity. In discussing tricyclic anti-depressants, Goodman and Gilman, 8th edition, at pages 411-412, "Significant side effects ... are common ... Most of these reactions involve anti-muscarinic effects of the drugs ... Clinical consequences of the anti-muscarinic effects include dry mouth and a sour or metallic taste, epigastric distress, constipation, dizziness, tachycardia, palpitations, blurred vision and urinary retention ..."

The anti-muscarinic activity of tricyclic anti-psychotics is generally somewhat less, but it is still significant. As stated in Goodman and Gilman at page 392, "blurring of vision commonly experienced with chlorpromozine may be due to an anticholinergic action on the ciliary muscle ... Decreased sweating and salivation are probably additional manifestations of the anticholinergic effects of the phenothiazines ..."

A mild level of anticholinergic activity in that generation of anti-psychotic drugs was regarded as a useful side effect. The primary action of those types of anti-psychotic drugs involved blockade of dopamine receptors, and that type of dopaminergic action caused Parkinson-like side effects; accordingly, the anti-cholinergic activity which was a secondary effect of those anti-psychotic drugs helped limit and control the Parkinson-like side effects caused by their dopamine-blocking activity.

It has been known for decades that some patients who are taking tricyclic anti-depressant drugs report that these drugs seem to alleviate some of their pain symptoms. Not surprisingly, there is a heavy correlation between chronic pain and depression; nearly anyone who suffers from constant chronic pain will become depressed, and anyone who feels seriously depressed almost always suffers even more, from a given level of pain.

The physiological basis for the apparent reductions in pain provided in some patients by tricyclic anti-depressant drugs has never been adequately understood, and it has been widely assumed that most such pain relief is probably just a byproduct of treating the patient's depression, and improving his or her mental state and outlook. To a large extent, that assumption has been supported by another factor, which indicates that drugs which have anti-muscarinic activity (i.e., which suppres the activity of ACh at muscarine receptors) should not be expected to reduce pain, because drugs which have the opposite effect (i.e., cholinergic agonists) are known to have pain-reducing activity. That factor was discussed above, under a separate subheading.

In addition to having anti-muscarinic activity as described above, a few TCAA compounds were reported to have some level of NMDA antagonist activity, in two isolated reports that appeared in the late 1980's.

Olney et al 1987 reported that a number of known anti-cholinergic drugs had relatively mild but potentially significant levels of NMDA antagonist activity. One compound having a TCAA structure (ethopropazine) was included in their survey; its NMDA antagonist potency is shown in Table 1, along with several other anti-cholinergic drugs that were also surveyed in those tests.

TABLE 1

BINDING OF ANTI-CHOLINERGIC DRUGS TO NMDA RECEPTORS

(from Olney et al 1987)

	Protective concentration, μM
Procyclidine	15
Ethopropazine	*25*
Trihexyphenidyl	125
Biperiden	200
Diphenhydramine	250
Scopolamine	> 3000

In Table 1, the "protective concentration" for each compound was the micromolar concentration of that compound which provided complete protection for neurons, in cell culture tests, against a 200 μM concentration of NMA (i.e., a racemic mixture of the D and L stereoisomers of N-methyl-aspartate; the D isomer, which makes up 50% of the racemic mixture, is highly toxic to neurons, while the L isomer is somewhat less toxic). Accordingly, a low value in Table 1 indicates relatively potent binding of a test compound to NMDA receptors; a high value indicates weak binding to NMDA receptors. For comparative purposes, phencyclidine had a value of 0.5, which was 30 times more potent than procyclidine, and 50 times more potent that ethopropazine. Ketamine had a value of 5, which was 3 times more potent than procyclidine, and 5 times more potent than ethopropazine.

One other article, Reynolds et al 1988, evaluated several anti-depressants for NMDA receptor activity, and reported that they can weakly inhibit the binding of dizocilpine (a highly selective NMDA receptor-binding agent, discussed below) to NMDA receptors. Reynolds et al tested five anti-depressants, and reported that under the test conditions used, those drugs had the IC_{50} values shown in Table 2.

TABLE 2

BINDING OF TRICYCLIC ANTI-DEPRESSANTS TO NMDA RECEPTORS

(from Reynolds et al 1988)

	IC50 (micromolar)
Desipramine	7.41 ± 1.32
Nortriptyline	21.0 ± 0.67
Imipramine	22.5 ± 2.44
Clomipramine	26.7 ± 1.51
Chlorpromazine	45.9 ± 11.5

In Table 2, IC50 values refer to "inhibitory concentrations" i.e., the concentration of a test compound that suppressed MK-801 binding by 50%. A low IC50 value indicates that a compound was relatively potent in blocking MK-801 binding to NMDA receptors; a high IC50 value indicates that a compound was relatively weak. For comparative purposes, ketamine showed an IC50 value of 1.02 ± 0.33 μM.

Accordingly, the results in Table 2 indicate that at least some of the TCAA compounds tested had detectable levels of NMDA binding activity; however, as with the Olney et al 1987 report, the NMDA blocking potency shown by even the strongest drugs tested was only a fraction of the NMDA binding activity of other well-known NMDA antagonist.

On the subject of binding to NMDA receptors by tricyclic compounds, it should be noted that the most potent and selective NMDA antagonist known is a tricyclic compound called dizocilpine, described in various US patents, including 4,064,139 (Anderson et al 1977) and 4,888,347 (Woodruff et al 1989). The maleate salt of dizocilpine is known as MK-801; although it is not safe for human use, it is the "gold standard" probe drug used in research involving NMDA receptors in cell culture or animal tests.

Dizocilpine is not a tricyclic alkyl-amine, since it does not have an alkyl-amine component. However, dizocilpine has a seven-member center ring flanked by two benzene rings, which is the same structure present in a number of tricyclic anti-depressants, including imipramine, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine and clomipramine.

Based on their structural similarity to MK-801, and based on test data already gathered for other tricyclic alkyl-amine compounds such as ethopropozine, it appears that a substantial number of already-approved, already-commercialized TCAA compounds are likely to have significant levels of NMDA receptor antagonist activity. It is indeed possible that the pharmaceutical companies which manufacture and sell such drugs may already have

tested the NMDA antagonist potency of the TCAA drugs they sell; however, since it is well-known that NMDA antagonists cause neurotoxic side effects, there do not appear to be any published reports addressing that issue. The only published reports the Inventors herein are aware of which explicitly state that certain TCAA compounds have any level of NMDA antagonist activity are Olney et al 1987, and Reynolds et al 1988, cited above.

MEMANTINE AND OTHER ADAMANTANE DERIVATIVES

Another class of NMDA antagonist compounds important in this invention include certain adamantane derivatives, including a drug known as memantine. Adamantane, a compound that occurs naturally in petroleum, is also called tricyclo-decane. It has a four-sided structure, comparable to a pyramid, wherein all four sides of the pyramid are formed by cyclohexane rings that share atoms with each other.

In the 1960s, researchers discovered that compounds in the adamantane family, especially an analog named amantadine, have some degree of anti-viral activity (US patents 3,328,251, Smith 1967; 3,391,142, Mills et al 1968). Amantadine was subsequently found to have muscle relaxant properties, and it was marketed in the US as a treatment for parkinsonism. Amantadine is currently available in the U.S., both as a generic drug and under the trademark SYMMETREL (sold by Endo Laboratories, Wilmington, Delaware).

Additional research on adamantane analogs revealed that 3,5-dimethyl-1-amino-adamantane (called memantine) has the same muscle relaxing effects as amantadine, and in some respects works better as a drug for treating patients with Parkinsonism. Accordingly, in the 1990s, memantine was approved for sale and public use in Europe, under the trademark AKATINOL. Based initially on anecdotal reports, it was also reported that memantine might be helpful in treating at least some types of dementia (e.g., Jain 2000).

About 10 years ago, it was reported that memantine has mild NMDA antagonist activity (Bormann 1989; Kornhuber et al 1994; also see US patent 5,061,703, Bormann 1991)). This led to several patent filings, in an effort to claim the potential use of memantine and amantadine in reducing neuronal damage associated with progressive neurodegenerative diseases (US 5,614,560, Lipton 1997) or AIDS dementia (US 5,506,231, Lipton 1996), and in treating neuropathic pain (US patent 5,334,618, Lipton 1994).

Neugebauer et al 1993, Eisenberg et al 1993, 1994, 1995, and Carlton et al 1995 also reported early research results on memantine for treating neuropathic pain; however, the accumulated reports on pain control are mixed at best, and several recent research

reports (e.g., Eisenberg et al 1998, Nikolajsen et al 2000) stated that at the dosages tested, memantine failed to provide any significant pain relief in human patients who were tested. Von Euler et al 1997 and Tzschentke et al 1999 also provide negative reports on the apparent lack of efficacy of memantine in treating certain other conditions.

Other reports state that memantine is highly promising, and may be effective in treating a host of neurological disorders. Such reports include Chen et al 1998, Jain 2000, Zinkevich et al 2000; also see Parsons et al 1999, written by employees of the Merz company. These reports all assert that memantine, at effective dosages, appears to be inherently safe and essentially free from the neurotoxic side effects that have plagued other NMDA antagonist drugs, due to the fact that the NMDA receptor "kinetics" of memantine are different from those of drugs such as MK-801; apparently, memantine releases and disengages from the NMDA receptor complex much more quickly than neurotoxic NMDA antagonists such as MK-801. Accordingly, at the present time, a concerted effort is being made by the manufacturers of memantine (Merz, a German pharmaceutical firm) to gain approval from the U.S. Food and Drug Administration (FDA) to market memantine in the US as a non-neurotoxic NMDA antagonist.

At least some of the claims which assert that memantine is free from neurotoxic effects are based on carefully limited dosages. Memantine proponents state that they have administered memantine to rats at dosages of 20 mg/kg, and did not find signs of neurotoxicity in the retrosplenial cortex (e.g., Chen et al 1998). That may be true, but the Applicants herein have tested memantine in rats at only slightly higher dosages, such as 25 mg/kg, and have seen clear and consistent evidence of neurotoxicity, such as vacuoles in neurons in the vulnerable parts of the brain. Accordingly, based on a number of factors too complex to describe in detail herein, and based on their experience in testing numerous candidate NMDA antagonists (including memantine), the Applicants herein remain convinced that memantine will be substantially safer, even when used at substantially higher (and therefore more effective) neuroprotective dosages, if it is coadministered with a safener agent, such as one of the classes of safener agents mentioned above.

THE ADRENERGIC TRANSMITTER/NEUROHORMONE SYSTEM

The other neurotransmitter-receptor system that must be taken into consideration, in the current invention, is called the "adrenergic" system. This system is discussed in Kandel et al, editors, *Principles of Neuroscience*, or in the *Encyclopedia of Neuroscience* (first

edition, edited by Adelman, 1987, or second edition, edited by Adelman and Smith, 1999).

Very briefly, the two molecules that serve as transmitters in the adrenergic system are norepinephrine (also called noradrenalin) and epinephrine (also called adrenalin). The receptors that are triggered by these molecules are divided into two classes, designated as alpha (α) and beta (ß). ß-adrenergic receptors are not of any particular interest herein; they are reviewed in, e.g., Strosberg 1995 and Liggett 2000.

α-adrenergic receptors are subdivided into the $\alpha 1$ and $\alpha 2$ classes. The $\alpha 2$ subclass, which is of direct interest herein, has been further subdivided into A, B, C, and D classes, but "little is currently known about the specific function mediated by the various subtypes" (Bylund 1995). Reviews that focus on the $\alpha 2$ receptor system include Stornetta et al 1995, Saunders et al 1999, and Rosin 2000.

Reviews that focus on drugs which react with $\alpha 1$ and/or $\alpha 2$ receptor subtypes include Eisenach et al 1996, Kamibayashi et al 1997 and 2000, Newcorn et al 1998, Frishman et al 1999, and Cotecchia et al 2000.

Two facts about $\alpha 2$ adrenergic agonist drugs (referred to herein simply as $\alpha 2$ agonists, for convenience) should be recognized and emphasized, since both facts are directly relevant to this invention. One fact is this: $\alpha 2$ agonist drugs have sedating effects; indeed, they are often referred to as "sedative-hypnotic" drugs (e.g., Levanen et al 1996). As such, they are used in both veterinary and human surgery, to help boost the depth and quality of anesthesia provided by a drug such as ketamine (e.g., Verstegen et al 1989; Nevalainen et al 1989; Moens et al 1990; Levanen et al 1996; Handa et al 2000). The ability to relax a patient or pet, and take them deeper into anesthesia while also minimizing certain unpleasant side effects of ketamine anesthesia (such as psychotic "emergence reactions") is useful and desirable, in anesthesia. However, it becomes a serious problem if a "sedating-hypnotic" drug must be taken every day to control chronic pain. The last thing a patient wants, when struggling with chronic pain, is to feel groggy, sedated, and semi-stuporous every day.

The second fact is this: $\alpha 2$ agonists substantially lower blood pressure. That is their main therapeutic use, i.e., reducing blood pressure in patients suffering from hypertension (high blood pressure). Reduced blood pressure can be useful in someone who needs it, but it can be very dangerous, and potentially even lethal, in someone who doesn't need it. Among other things, reduced blood pressure causes dizziness, which can be dangerous for anyone, and which is especially dangerous in elderly patients, since dizziness can lead to a

fall, and a fall by an elderly patient often results in a broken hip or other severe injury.

Accordingly, both of those two facts teach directly away from the current invention, which involves the chronic use of α2 agonists to help control neuropathic pain.

Beyond those facts, anyone approaching a study of the adenergic system for the first time should recognize and be forewarned that a huge amount of research is being done on that system, because (i) it is not yet well understood, and (ii) it is extraordinarily complex, multi-faceted, and apparently paradoxical in many respects. The testing of drugs that can affect one or more components of the adrenergic system tends to be unusually complex and risky, since adrenergic drugs tend to pose unusually high risks of triggering unwanted side effects.

Several selective α2 agonist drugs (including clonidine, iodoclonidine, guanabenz, guanfacine, xylazine, lofexidine, medetomidine, dexmedetomidine, tizanidine, rilmenidine, azepexole, α-methyldopa, and α-methylnoradrenaline) have been discovered which activate α2 receptors with substantially higher affinity than they have for α1 receptors.

As noted above, most α2 agonist drugs of commercial interest are used clinically as anti-hypertensive drugs, to help reduce blood pressure in patients suffering from hypertension. At least two α2 agonists, clonidine and lofexidine, also have been tested by researchers to evaluate their ability to help reduce withdrawal symptoms in people addicted to cigarettes or opiates (e.g., Washton et al 1983; Siegel et al 1985; Segal 1985; Green and Cordes 1989). α2 agonists have also been used as adjuncts in surgical anesthesia, as discussed above, and they have been injected into spinal regions, using intrathecal or epidural injections, for pain relief. However, they have never previously been used as daily treatments for chronic pain.

Indeed, the fact that α2 agonist drugs are commonly used by anesthesiologists, as sedative-hypnotic agents which can help relax patients before surgery, teaches directly away from the current invention. This invention requires chronic, daily use of a drug combination as disclosed herein. Therefore, known and substantial sedating and/or hypnotic activities of a drug being considered for this type of chronic, daily use would be highly adverse to the goal of identifying a non-sedating treatment for chronic pain.

Accordingly, one object of this invention is to disclose that several classes of drugs which have significant yet relatively mild activity as NMDA antagonists have some degree of efficacy in relieving neuropathic pain. However, any pain relief provided by these drugs, used alone, is relatively brief, and is accompanied by unwanted side effects when

administered at the dosages needed to substantially relieve neuropathic pain.

A much more important object of this invention is to disclose that when a mild NMDA antagonist (such as procyclidine, ethopropazine, or memantine) is co-administered with an $\alpha 2$ adrenergic agonist, such as clonidine, the two drugs mutually potentiate one another's ability to relieve neuropathic pain, in a manner which provides sustained and effective neuropathic pain relief, at a low dose of each agent that is below its threshold for producing any adverse side effects.

Yet another object of this invention is to disclose a unitary dosage form (such as a tablet, capsule, or skin patch) containing both an $\alpha 2$ adrenergic agonist drug and a mild NMDA antagonist (such as procyclidine, ethopropazine, or memantine), where each drug is present at a dosage which allows the combination to effectively control neuropathic or other chronic pain, without causing sedation, excessive reduction of blood pressure, cognitive or memory disruptions, or other undesired neurological or physiological side effects.

These and other objects of this invention will become more apparent through the following summary, drawings, and description of the preferred embodiments.

SUMMARY OF THE INVENTION

This invention discloses that a combination of two drugs, from two different and previously unrelated categories, provides effective and long-lasting relief from neuropathic pain. Both drugs can be taken orally, in a convenient, painless, non-invasive manner that does not require injections.

One drug in this combination is an $\alpha 2$ adrenergic agonist, exemplified by clonidine. These drugs, normally used to control high blood pressure, have been used in a few cases for pain relief, but only by means of intrathecal injection (i.e., injection directly into spinal cord fluid, to avoid dangerous and potentially lethal reductions in blood pressure, which might occur if a high dose of an $\alpha 2$ agonist is injected into non-CNS tissue). These drugs have not previously been regarded as promising candidates for use in treating neuropathic or other chronic pain, since they are recognized as sedative-hypnotic agents, and sedation is a highly undesirable trait in a drug that must be taken every day.

The other drug in the pain-relieving combination is an agent that has NMDA antagonist properties which can be described using terms such as mild, minimally toxic, and/or inherently safe (or safened). Three categories of such drugs have been identified and

shown to work exceptionally well in reducing neuropathic pain for prolonged periods, when coadministered with clonidine. The first such category includes certain aryl-cyclo-alkanolamine (ACAA) drugs with NMDA antagonist activity, such as procyclidine and biperiden. The second category includes certain tricyclo-alkylamine (TCAA) drugs with NMDA antagonist activity, such as ethopropazine. The third category includes certain adamantane derivatives with NMDA antagonist activity, such as memantine.

Tests by the Applicants have shown that none of these drugs, by itself, can provide effective relief for neuropathic pain; at the doses required to provide substantial short-term relief, they cause serious adverse side effects, and any pain relief they can provide, by themselves, is relatively brief and short-lived.

However, when one of these drugs is administered together with an $\alpha 2$ adrenergic agonist such as clonidine, the two drugs acting together mutually potentiate one another's neuropathic pain-relieving action, and provide potent and sustained neuropathic pain relief, even when each agent is administered at a low dosage that is below its threshold for causing adverse side effects.

Accordingly, these results indicate that combining selected drugs from two different classes can provide safe and effective relief of neuropathic pain and possibly other types of chronic and/or intractable pain, at dosages which are so low that they do not pose serious risks of adverse side effects.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURES 1 through 8 are graphs showing the results of tests using a standard model of neuropathic pain, involving the hind legs of rats, and their response to a warming light that was shone on the sole of the animal's hindpaw. In all graphs, open circles indicate data from "ligated" limbs, in which the sciatic nerve was chronically irritated by a loop of suture material that was surgically placed and then tightened around the nerve. Filled circles indicate "control" data, from sham-operated limbs that did not suffer any chronic irritation. Rapid lifting of a ligated paw after the warming light commenced indicates that the paw was hyper-sensitized to pain signals.

In graphs where the open circles are substantially lower than the filled circles, the drug treatment was not effective in controlling and reducing the neuropathic pain response. An example is provided in FIG. 1, which is a "baseline" control using a saline injection rather than a drug.

If a drug treatment was effective in reducing and controlling the neuropathic pain response, the vertical gap between an open circle (ligated limb) and a dark circle (non-ligated limb) was relatively small. The graphs in FIGS. 2 through 5 show that each individual agent, when tested by itself at varying dosages (clonidine, in FIG. 2; procyclidine, in FIG. 3; ethopropazine, in FIG. 4; memantine, in FIG. 5), could provide some level of pain relief, but only at high dosages which caused behavioral side effects, and only for a short time.

The graphs in FIGS. 6 through 8 show that a combination of clonidine, plus any one of the selected mild NMDA antagonists, provided much better and longer-lasting pain relief than either drug could provide by itself. In addition, comparison of the effective dosages in these tests against the same dosages in FIGS. 2 through 5 show that the combination worked well, even at very low dosages of both agents that were ineffective when administered by itself.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

This invention involves the use of a drug combination for treating chronic and/or intractable pain, such as neuropathic pain. The drug combination requires two distinct types of drugs.

The first component is an α2 adrenergic agonist drug, such as clonidine, iodoclonidine, guanabenz, guanfacine, xylazine, lofexidine, medetomidine, dexmedetomidine, tizanidine, rilmenidine, azepexole, α-methyldopa, and α-methyl-noradrenaline.

Clonidine (which is one of the most well-known and widely used α2 agonist drugs) is regarded herein as a "benchmark" drug, and it is a "selective" α2 agonist drug, but it is not regarded as a "highly selective" α2 agonist drug. The phrase "highly selective α2 agonist" refers to an α2 adrenergic agonist drug which has substantially higher selectivity for α2 receptors (and substantially lower affinity for α1 receptors) than clonidine. Published reports have stated that highly selective α2 agonists include dexmedetomidine, guanfacine, and azepexole, and may also include lofexidine and various other α2 agonists as well. In general, "selective" or "highly selective" α2 agonists are preferred, since they pose lower dangers of unwanted side effects. Accordingly, highly selective α2 agonists are regarded as promising candidates for evaluation in pain-controlling combinations as disclosed herein.

In addition, it must be recognized that a major physiological effect of clonidine (and

most other known α2 agonist drugs) is their ability to reduce blood pressure. That is their normal medical use, and it is useful in patients suffering from hypertension (high blood pressure). However, reductions in blood pressure are likely to be unwanted, and even potentially dangerous, in patients who do not suffer from hypertension, and who instead are suffering from neuropathic or other chronic pain. Accordingly, α2 agonist drugs with lower levels of hypotensive activity than clonidine are also regarded as promising candidates for evaluation in pain-controlling combinations as disclosed herein. Published reports indicate that lofexidine and guanfacine both fall within this criterion, and various other α2 agonists may also qualify.

Although the Applicants are not aware of any publication that systematically ranks or quantifies numerous α2 agonists in terms of α2 selectivity, potency in reducing blood pressure, severity or absence of side effects, and ability to penetrate mammalian blood-brain barriers, such information is provided, in scattered form, in various locations (e.g., Goodman and Gilman 1990 at page 308; Ruffolo et al 1993 at page 264; Doze et al 1989 at page 75).

In addition, evaluation of these relevant properties in any known or hereafter-discovered α2 agonist can be carried out with routine experimentation, using conventional procedures. Such tests include competitive binding assays to evaluate selectivity for α1 and α2 receptors; tests on both normal and hypertensive lab animals, to evaluate hypotensive activity; and analysis of CNS tissue following administration of radiolabelled drugs, to evaluate BBB permeability. Accordingly, based on the teachings herein, methods are provided for screening the α2 agonist drugs listed herein, or any other α2 agonist drugs which are currently known or hereafter discovered, and determining which ones will have the best profile of benefits vs. unwanted side effects, when coadministered with an ACAA drug which has NMDA antagonist activity, to relieve neuropathic or other chronic pain as disclosed herein.

The second component of the pain-controlling mixtures disclosed herein is an NMDA antagonist drug which has mild, minimally toxic, and/or inherently safe (or safened) activity at NMDA receptors. This type of second component can be selected from the following classes: (1) an aryl-cyclo-alkanolamine (ACAA) compound with some level of NMDA antagonist activity, such as procyclidine, biperiden, or trihexyphenydyl; (2) a tricyclo-alkylamine (TCAA) drug with some level of NMDA antagonist activity, such as ethopropazine or desipramine; and, (3) an adamantane derivative with some level of NMDA

antagonist activity, such as memantine.

These drugs are likely to be used over long spans of time, such as months or even years, possibly for the entire remaining life of the patient. Instead of being a "cure" for neuropathic or other chronic pain, which would permanently alter and correct damaged or dysfunctional neuronal circuitry that causes the neuropathic or other chronic pain, this invention discloses a treatment and control regimen, which can help the affected patient suppress and control the chronic pain, with minimal unwanted side effects such as sedation.

Since these drugs are likely to be used on a daily basis (ranging from once per day, up to several times per day, depending on the severity of the condition being treated), both drugs should be in a form suited for noninvasive and painless adminstration. Such modes of administration include, for example, oral ingestion of a tablet, capsule, or liquid, or use of a skin patch or other "transmembrane" route.

It is not asserted that the drug combinations disclosed herein will be completely free of any and all side effects, in all patients. Instead, this disclosure asserts that: (i) this drug combination allows the use of relatively low dosages of both constituent drugs, when they are coadministered with each other; and, (ii) the use of relatively low dosages of both constituent drugs strongly indicates that any adverse side effects will be minimized, and will be fully acceptable to large numbers of patients. Indeed, one of the most remarkable and valuable traits of the drug combination disclosed herein is that these two classes of drugs, when administered together, appear to be highly potent and effective in reducing neuropathic pain, even when each drug is administered at dosages which are only a fraction of the dosages that begin to exert detectable behavioral or other effects in treated animals.

As used herein, the phrase "*unacceptable* side effects" refers to side effects which, in a particular patient or class of patients, rise to a level of unpleasantness which that patient (or class of patients) regards as outweighing the benefits of the treatment. Clearly, dosages and frequency of administration will vary substantially between different patients; patients who are suffering from nearly unbearable intractable pain are likely to take high doses of both drugs, four or more times each day; by contrast, patients who are suffering from minor annoyances will take lower dosages, only once or twice each day. Accordingly, the acceptability of any side effects a drug combination as disclosed herein might cause, in a particular patient or class of patients, must be viewed in light of the pain-relieving benefits it provides for that patient or class of patients.

ANIMAL TEST DESIGN AND RESULTS

All of the graphs in FIGS. 1-8 pertain to the effects of various drug treatments on measurable pain-sensitive responses in test animals (rats). FIG. 1 shows the results of saline controls, which provided no pain relief. FIGS. 2 through 5 displays the results of a single drug (clonidine, procyclidine ethopropazine, or memantine, respectively). FIGS. 6 through 8 display the results of two-drug combinations.

In all experiments, one hind limb of the rat has undergone a surgical operation in which a loop ("ligature") of suture material was placed around the sciatic nerve and gently tightened. Over the course of several days, this caused chronic irritation to the nerve, driving it into a "hyper-sensitized" condition of the type which occurs in damaged neuronal circuits that cause neuropathic pain in humans. The other hind limb of each rat did not receive any operation, and served as a control condition.

After the nerve ligation operation, a waiting period of 8 days elapsed, to allow the ligated limb to reach a peak of hypersensitized chronic irritation of the ligated sciatic nerve. This sciatic nerve model was first described by Bennet and Xie 1988, and is widely regarded as a useful animal model for studying neuropathic pain.

To test the degree of sensitivity in the ligated limb vs. the unoperated limb, a beam of light (thermal stimulus) is applied to the soles (i.e., the undersurface area which is not covered by fur) of the hind paws, by shining a focused beam of light onto the sole, through the glass floor of a testing chamber. This beam was sufficiently hot to generate some discomfort, without posing any risk of burning the paw. The number of seconds that elapsed after commencement of the thermal stimulus, until the rat lifted up the paw, were detected electronically and recorded automatically.

Each limb is tested initially for thermal pain sensitivity, before the ligation operation is performed (pre-surgery), to ensure that both limbs had the same degree of pain sensitivity. After 8 days following surgery, each limb was tested again, before any treatment was given (pre-treatment), to ensure that the nerve ligature successfully provoked a hyper-irritable condition in the ligated limb. After drug treatment (at time = 0, on the graphs), each limb was tested for thermal pain sensitivity at hourly intervals, for 4 hours.

The graph in Fig. 1 depicts the level of pain sensitivity in each limb under control conditions, when a saline injection instead of an active drug was administered. In all graphs, open circles indicate data from ligated limbs, and filled circles indicate control data, from sham-operated limbs that did not have any ligatures to cause chronic irritation.

Rapid lifting of a ligated paw indicates that the paw was hyper-sensitive. If a large vertical gap occurs between the ligated limb (open circle) and the control limb (closed circle), such as shown in FIG. 1 at all times, this indicates that (i) the ligated paw was indeed suffering from a hyper-irritable neuropathic pain condition, and (ii) the drug treatment was not effective in reducing and controlling the response to the painful stimulus. After saline (control) treatment, there was no change in pain sensitivity in either limb, as indicated by the fact that the open circles (ligated limbs) and dark circles (unoperated limbs) continued to be widely separated, consistently showing more rapid paw withdrawals in the ligated limbs, following thermal stimulus, at each hourly interval.

The graphs in FIG. 2 show the pain sensitivity in each limb following intraperitoneal injection of clonidine, at three dosages (0.025 mg/kg, 0.05 mg/kg or 0.075 mg/kg). At the two lower doses, clonidine showed no significant relief of pain. At the highest dose, there was significant and relatively sustained neuropathic pain relief; however, at that dosage of clonidine, the rats displayed significant sedation and loss of motor activity and control, as described in Example 5. In at least some and probably even most humans, a comparable dose of clonidine would very likely produce serious unwanted sedation, and a lowering of blood pressure to an unacceptable and potentially dangerous degree.

The graphs in FIG. 3 show that intraperitoneal injection of procyclidine, at three different dosages, did not provide adequate and lasting relief from pain sensitivity. At the lowest dosage used (10 mg/kg, shown in FIG. 2A), the procyclidine had no apparent effect at all. At 25 mg/kg, shown in Fig. 2B, the procyclidine had some effect after 1 hour, but that response in ligated limbs did not reach or even closely approach the response times in unoperated limbs; in addition, even that mild effect shown at 1 hour dropped off substantially within 2 hours. At the highest dosage tested (50 mg/kg, shown in FIG. 3C), complete relief from neuropathic pain was seen at the 1 hour testing time. However, this level of pain relief dropped off substantially by the second hour; and, just as importantly, a comparable dose in humans would very likely cause substantial discomfort (such as dry mouth, blurred vision, and gastrointestinal disturbances) in at least some patients, due to the strong anticholinergic action of procyclidine.

The graphs in FIG. 3 should be compared to the graphs in FIGS. 6A and 6B, which show that when procyclidine and clonidine were administered together, the combination provided sustained relief of neuropathic pain. Just as importantly, these graphs show that effective and sustained pain relief was provided at relatively low dosages, which did not

cause any significant reduction in pain when each drug was administered by itself. In Fig. 6A, a very low dose of procyclidine (10 mg/kg) plus a very low dose of clonidine (0.025 mg/kg) caused a substantial decrease in the vertical gaps between the two curves. While peak relief was seen at 2 hours, a substantial degree of pain relief was still evident at 4 hours, when the testing stopped. Fig. 6B shows that if the dose of procyclidine was increased to 25 mg/kg (which was still ineffective, by itself) and the dose of clonidine was held to a low dose (0.025 mg/kg), effective and sustained relief of neuropathic pain was achieved.

The graphs in FIG. 4 show that IP injection of ethopropazine alone, at dosages ranging from 10 to 30 mg/kg, did not significantly change the pain sensitivity in either limb, as evidenced by the fact that the open (treated) circles did not closely approach the dark (control) circles. The graph in FIG. 4D shows that ethopropazine at 50 mg/kg significantly changed the level of pain sensitivity in the ligated limb; however, a comparable dose in humans would very likely cause substantial discomfort (dry mouth, blurred vision, gastrointestinal disturbances) due to the strong anticholinergic activity of ethopropazine.

An important feature of FIGS. 4B and 4C is that both curves rose, substantially, at the 2 and 3 hour testing times. This indicates that ethopropazine, by itself, showed effects in reducing neuropathic pain (lower curve, open circles), and in reducing general (non-neuropathic) pain (upper curve, closed circles). That is a noteworthy result, since ethopropazine has not previously been recognized as having significant pain-relieving activity.

The effects of co-administering clonidine (0.025 mg/kg) together with ethopropazine, at doses of 10 mg/kg or 20 mg/kg, are shown in FIG. 7. These graphs show that the combination provided significant and sustained relief from neuropathic pain, especially at the 2nd and 3rd hourly tests. These results, while not ideal, are highly promising, and more than sufficient to justify the assertion that when those two drugs were administered together, at relatively low dosages, the pain-relieving results they achieved were superior to the results that could be provided by either drug alone, at that same dosage level.

The graphs in FIG. 5 show that IP injection of memantine alone, at 2.5 mg/kg (FIG. 5A) did not significantly change the pain sensitivity in either limb, as evidenced by the fact that both the open circles and dark circles remain at their pre-treatment vertical levels at

each post-treatment interval. At all times, the gap between the open and dark circles remained widely separated. At twice that dosage, 5 mg/kg (FIG. 5B), memantine showed some slight effects in reducing neuropathic pain, at the 2nd and 3 hours post-treatment. That effect had worn off completely by the 4th hour. FIG. 5C shows that IP injection of memantine at 10 mg/kg caused a climb to a peak of highly effective pain relief at 2 hours post-treatment; however, that pain relief had dropped off substantially by the 3rd hour, and had disappeared completely by the 4th hour. No higher doses were tested, since it was felt by the Applicants that even the 10 mg/kg dosage (which was nearly half the dosage that began to show serious neurotoxic side effects in the brains of other treated animals) was already too high to offer a feasible and practical daily treatment for chronic pain.

When clonidine (0.025 mg/kg) was coadministered with memantine (2.5 mg/kg), the results, shown in FIG. 8, clearly indicate that the combination was highly effective in providing sustained relief from neuropathic pain. Indeed, the extent of pain relief was still so high after 4 hours that additional testing was repeated after 6 hours, at which time the pain reduction was still significantly better than the pre-treatment baseline.

In this test, each drug was administered at a dose that, by itself, did not offer any detectable pain relieving effects, and did not pose any serious risk of neurotoxic side effects, or cognitive or behavioral impairments. The 2.5 mg/kg dosage of memantine corresponds to FIG. 2A, which clearly shows that at 2.5 mg/kg, memantine by itself offered no protection whatever against neuropathic pain. The 0.025 mg/kg dosage of clonidine corresponds to FIG. 3A, which shows that, at that dosage, clonidine by itself also was totally ineffective in providing any relief from neuropathic pain.

MODES OF ADMINISTRATION

The mixtures of this invention may be administered by any suitable route which will introduce the intended drug(s) into the bloodstream. As noted above, preferred modes should use painless non-invasive means, such as oral ingestion of tablets, capsules, or liquids, or transmembrane routes, such as skin patches, nasal sprays, lozenges, penetrating ointments, etc. Intramuscular, intravenous, or other forms of injection, as well as subcutaneous implantation of slow-release devices or formulations or osmotic mini-pumps, are also possible, but they are less convenient and more painful and troublesome than noninvasive modes such as pills or skin patches.

All such modes of administration are all well known in the pharmaceutical arts, and

typically require a pharmaceutically acceptable carrier in addition to the active ingredients. In making the pharmaceutical mixtures disclosed and claimed herein, the active ingredients will usually be mixed with and diluted by a carrier, or enclosed within a carrier such as a capsule. When the carrier serves as a diluent, it may be a solid, semisolid or liquid material which acts as a vehicle, excipient or medium for the active ingredients. Thus the composition can be in the form of tablets, pills, powders, lozenges, chewing gum, cachets, elixirs, emulsions, solutions, syrups, suspensions, aerosols (as a solid or in a liquid medium), ointments containing for example up to ten percent by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

For oral administration, the compositions of this invention can be admixed with carriers and diluents molded or pressed into tablets, or enclosed in gelatin capsules, or otherwise loaded into digestible plastic or other capsules. Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, gelatin, syrup, methyl cellulose, methyl- and propyl-hydroxybenzoates, talc, magnesium, stearate, water, mineral oil, and the like. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions may be formulated so as to provide rapid, sustained, or delayed release of the active ingredients after administration to the patient, by employing procedures well known in the art.

The compositions are preferably formulated or packaged in a unit dosage form, each dosage unit containing an effective amount of both (i) one or more mild/minimally toxic/inherently safened NMDA antagonists, and (ii) a selected $\alpha 2$ agonist. The term "unitary dosage form", as used herein, has two meanings. One meaning refers to physically discrete units (such as capsules, tablets, or skin patches) which are suitable as unitary dosages for human subjects (or for pets, etc.) wherein each unit (each pill, skin patch, etc.) contains a predetermined quantity of each of the two active drugs discussed herein. In this type of unitary dosage form, the dosages of both drugs are predetermined, and are designed to safely produce the desired therapeutic effects, in most patients.

The second meaning of "unitary dosage form" refers to a liquid, dry powder, or similar formulation which is not divided into discrete units, but which contains each of the

two active drugs discussed herein at predetermined concentrations which allow desired dosages of both drugs to be dispensed conveniently by referring to a fixed volume of the liquid or powder. As one example, a liquid containing two active drugs in a carrier can be provided in a unitary dosage form, if the desired dosage of each drug can be taken by ingesting a fixed quantity (such as a single teaspoon, tablespoon, etc.) of the liquid. Similarly, a powdered formulation of two drugs can be provided in a unitary dosage form, if the desired dosage of each drug can be taken by stirring a teaspoon, tablespoon, or "scoop" (if a plastic scoop is provided in the container) of the material into a suitable liquid which is then swallowed.

Alternately or additionally, non-divided preparations such as liquids, aerosols, or powders can be packaged inside unitary-dosage container devices which are designed to dispense a predetermined volume of material each time the device is used. Examples of unitary-dosage dispensing containers include: (i) inhaler devices, which release a predetermined amount of medicine (such as for treating asthma) into the mouth or nasal sinuses each time the device is squeezed; and, (ii) plastic bottles which are provided with a small chamber near the outlet, wherein the chamber is provided with a liquid-level marker that indicates how much liquid should be squeezed into the chamber for a proper dose of the liquid. By controlling the concentration of each drug in the liquid, aerosol, powder, or other preparation in a dispenser, unitary dosage of drug mixtures can be provided by such devices.

In either case, a "unitary dosage form" of a non-divided material such as a liquid, aerosol, or powder can be provided by controlling the concentrations of both drugs carried by the material, so that administration of a controlled volume of the material will provide the desired unitary dosage.

The amount of either drug, in a unitary dosage formulation, will depend on factors such as the severity of the pain condition being treated in a particular patient, and the the amount and potency of the other drug in the same formulation. These drug cocmbinations are (or are likely to be) available only with a prescription from a physician; they are not available over-the-counter. Accordingly, the preferred dosage and mode of administration of the two drugs, in combination, will be under the control of a qualified physician, who can evaluate all relevant factors for any specific patient (including the age, weight, and response of the individual patient, the severity of the patient's symptoms, the chosen route of administration, etc.). In addition, it is standard practice in treatments of this nature for a

physician to administer an initial dosage for a test period such as two weeks, and subsequently adjust the dosage depending on the results observed during the test period. Therefore, the dosage ranges provided below are intended to provide general guidance and support for the teachings herein, but are not intended to limit the scope of the invention.

In general, the preferred dosage of an $\alpha 2$ agonist will usually lie within the range of from about 0.001 to about 1000 mg, more usually from about 0.01 to about 500 mg per day. The amount of the NMDA drug may vary over a wider range, depending on the level of NMDA antagonist activity provided by the selected drug.

The terms, "drug", "agonist", and "antagonist," as used herein, includes so-called "pro-drugs" which are administered in a form that is known and intended to be metabolized, inside a patient's body, into a different form which has a specific desired activity. As an example, α-methyldopa is a pro-drug form of an $\alpha 2$ agonist; the dopa form is actively transported into the CNS, which is desirable, and then enzymes inside the CNS convert the dopa form into α-methyl-norepinephrine, which is the active $\alpha 2$ agonist form of the drug. In such cases, both α-methyldopa and α-methyl-norepinephrine would be regarded as $\alpha 2$ agonist drugs for the purposes of this invention.

Various salts and isomers (including stereoisomers) of the drugs listed herein can be used. The term "salts" can include alkali metal salts as well as addition salts of free acids or free bases. Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include inorganic acids such as hydrochloric, sulfuric, or phosphoric acid, and organic acids such as acetic, maleic, succinic, or citric acid, etc. Alkali metal salts or alkaline earth metal salts include, for example, sodium, potassium, calcium, or magnesium salts. All of these salts (or other similar salts) may be prepared by conventional means. The nature of the salt or isomer is not critical, provided that it is non-toxic and does not substantially interfere with the desired pharmacological activity.

ANALOGS AND DERIVATIVES

As noted above, a number of anti-cholinergic drugs are known which have structures that closely resemble ACAA or TCAA drugs, but which do not fall squarely within the term "aryl-cyclo-alkanol-amine" or "tricyclo-alkylamine". These drugs are referred to herein a "analogs" of ACAA or TCAA drugs. Examples of ACAA analogs include mepenzolate (sold under the trademark CANTIL), piperodolate (DACTIL), isopropamide (DARBID), thiphenamil (TROCINATE), adiphenine (TRASENTINE), and dicyclomine

(BENTYL). The term "analog" is used herein in the conventional pharmaceutical sense, to refer to a molecule that structurally resembles a referent molecule (such as procyclidine, ethopropazine, etc.) but which has been modified in a targeted and controlled manner to replace one or more specific substituents of the referent molecule with an alternate substituent, thereby generating a molecule which is structurally similar to the referent molecule. Synthesis and screening of analogs, to identify slightly modified versions of a known compound which may have slightly improved traits (such as higher potency and/or selectivity at a specific targeted receptor type, greater ability to penetrate mammalian blood-brain barriers, etc.) is an approach that is well known in pharmaceutical chemistry.

Similarly, the term "derivative" is used herein to describe a compound which is derived from a starting compound, in the process used to create a similar but slightly different drug which resembles the starting compound but which does not fall squarely within the ACAA or TCAA boundaries.

ACAA and TCAA analogs and derivatives are covered by the claims below, but only if and to the extent that they have the four essential traits and activities of ACAA or TCAA drugs which are of interest herein (i.e., pharmaceutically acceptable; substantial anti-muscarinic activity; substantial NMDA antagonist activity; and, therapeutic efficacy against neuropathic pain when co-administered with an $\alpha 2$ adrenergic agonist drug). If some particular ACAA or TCAA analog or derivative does not have all four of those traits, it is of no interest herein, and it is not intended to be covered by the claims.

ISSUES OF BBB PERMEABILITY

It is well-known that large numbers of NMDA receptors and $\alpha 2$ adrenergic receptors are present on neuronal surfaces both inside the CNS, and outside the CNS. A major difference and distinction between those two classes of neurons relates to the so-called "blood-brain barrier" (BBB), which exists in all vertebrate animals. Except for a few minor specialized classes of neurons (such as those referred to as "circumventricular organ" neurons), a general distinction between CNS versus non-CNS neurons is that most CNS neurons have their cell bodies (i.e., the thickest part of the neuron, which contains the nucleus) located in tissue that is protected by the BBB, while most non-CNS neurons (which are involved in neuronal circuits usually called peripheral, autonomic, sympathetic, parasympathetic, etc.) have their cell bodies located in tissue that is not protected by the BBB. However, since many types of both CNS and non-CNS neurons have axons and other

fibers that pass through the BBB, to help implement CNS control over muscles, organs, and other tissues, it is not entirely accurate to refer to CNS neurons as being protected by the BBB while CNS neurons are not.

The BBB is not a single barrier in the form of a membrane surrounding the brain and spinal cord. Instead, it arises from the fact that the capillaries which service CNS tissue have special structures, with "tight junctions" between the endothelial cells that make up those capillary walls. These "tight junctions" prevent a wide variety of molecules from passing through the capillary walls in CNS tissue, and thereby prevent CNS neurons from being contacted and potentially disrupted by such molecules. Recent monographs and review articles that discuss the physiology and functioning of the BBB include Brightman et al 1992, Rubin 1999, Pardridge 1999, Kniesel et al 2000.

Since NMDA receptors and $\alpha 2$ adrenergic receptors are present in large numbers both inside and outside the BBB, it is not yet known whether or to what extent the benefits of the invention disclosed herein might be improved (such as by achieving longer duration of pain relief, etc.), in one or more classes of patients, by using: (i) an ACAA or TCAA drug or analog thereof which has somewhat lower, or somewhat higher, BBB permeability levels than a known ACAA or TCAA drug such as procyclidine or ethopropazine, and/or, (i) an $\alpha 2$ adrenergic agonist which has somewhat lower, or somewhat higher, BBB permeability levels than a known $\alpha 2$ agonist such as clonidine.

That additional knowledge, even if it may be able to someday enhance and improve some embodiments of this invention for some patients, is not essential to carrying out this current invention. Instead, this invention is already fully enabled, by the disclosure that certain combinations of already-known drugs having already-known properties can act synergistically, to provide effective, sustained, and apparently non-sedating relief from at least some types of neuropathic pain, even at low dosages of each drug.

Nevertheless, the possibility of further improving this invention should not be neglected, even at this very early stage of disclosure. Accordingly, one approach to improving this invention, possibly for large numbers of affected patients or possibly for only limited categories of patients, involves further analysis to evaluate the pain-relieving effects provided by specific drugs, combined as disclosed herein, that have greater or lesser BBB permeability than procyclidine and clonidine.

In this type of work, it should be recognized that various methods and models have been developed, for animal testing of BBB permeability; these are reviewed in, for

example, Bonate 1995. In addition, early efforts to create *in vitro* (cell culture) models for evaluating BBB permeability of candidate drugs are discussed in Townsend et al 1995 and DeBoer et al 1999.

Other articles focus more specifically on various methods of getting candidate drugs through the BBB and into brain tissue. Most such methods generally fall into one of three categories:

(1) manipulating the BBB to render it more permeable for a brief period of time, such as by intravenous injection of an osmotic-manipulating solution shortly before an anti-cancer drug is injected into a patient with brain cancer;

(2) binding "passenger" compounds to antibodies that can bind to and exploit a BBB transport system such as the transferrin system; and,

(3) modifying candidate drug compounds, to increase their lipophilicity or otherwise increase their ability to penetrate the BBB.

All of these methods are discussed in various review articles, including Langer 1989, Abbott 1996, Begley 1996, Pardridge 1998, Kroll et al 1998, and Rochat et al 1999, and in numerous other research reports which are cited in these review articles. Clearly, for long-term use of a drug designed to control chronic pain, the third approach listed above holds the most promise.

Since it is a well-known principle that drugs which are relatively lipophilic tend to cross mammalian blood-brain barriers more readily and in higher concentrations, one of the most commonly used approaches to increasing BBB permeability of a candidate drug involves modifying a known compound (which can be regarded as the initial, starting, or "referent" compound; procyclidine and clonidine offer examples) in a manner that increases its BBB permeability, by modifying the known/starting compound in a manner that slightly increases its lipophilicity. This can be done by various methods known to those skilled in organic chemistry, such as by modifying pendant groups that are bonded to the central structure of a molecule. As examples, a lower alkyl group might be added as a pendant group to a referent compound; a slightly longer alkyl group might be substituted for one that is already present; or an atom or group with a lower degree of polarity might be substituted for a highly polar atom or group. Any of these substitutions (or various others, as discussed in articles such as Kroll et al 1998, Rochat et al 1999, etc., cited above) can create analogs that are more lipophilic, and that are likely to be more readily able to penetrate blood-brain barriers, than the starting/referent compound.

Conversely, if it is desired to create and evaluate candidate drugs that are less lipophilic, that can be done by a chemical modification which is the opposite of an approach listed above.

The lipophilicity of candidate compounds often can be predicted with fairly good accuracy by a skilled chemist, just by considering the constituents of the molecule, especially if the molecule is a related analog of another compound with a known level of lipophilicity. Regardless of the accuracy of such a prediction, the lipophilicity of any candidate drug can be measured using simple tests, such as measuring how much of the compound goes into the organic phase, and how much goes into the water phase, when a fixed amount of the compound is stirred into a container that contains both water and a non-polar organic solvent.

Accordingly, analogs and derivatives of any known or hereafter-discovered drug can be created which are either more lipophilic, or less lipophilic, than existing known drugs. Such analogs and derivatives offer good candidates for evaluation in animal tests, to identify candidate compounds that penetrate the BBB either in somewhat higher concentrations, or in somewhat lower concentrations, using methods such as described in Bonate 1995.

Numerous pharmaceutical companies have already patented many hundreds and possibly even thousands of analogs of their best-known ACAA and TCAA drugs, and their best-known $\alpha 2$ adrenergic agonists. For various reasons, those compounds were not chosen for commercialization to treat Parkinson's disease (in the case of ACAA or TCAA drugs) or hypertension (in the case of $\alpha 2$ adrenergic agonists). However, now that an entirely separate and different therapeutic use (or potential class of uses) for such drugs has been disclosed, the numerous already-known but not-previously-commercialized variants of the previously-commercialized ACAA or TCAA drugs and $\alpha 2$ adrenergic agonists can be reevaluated, using no more than routine experimentation, to determine whether they may be more effective (longer lasting, fewer side effects, etc.) than the previously-commercialized ACAA or TCAA drugs and $\alpha 2$ adrenergic agonists, in treating any particular type or class of neuropathic pain or other chronic or intractable pain.

EXAMPLES

EXAMPLE 1: TEST PROCEDURES AND CONTROL RESULTS

The first set of *in vivo* tests involved sciatic nerve ligation in rats, using procedures

described in Bennett and Xie, *Pain 33*: 87-107 (1988). This test involves surgically placing and tightening a loop of suture material around the sciatic nerve in one hind leg of a rat; the other hind leg serves as a control. Within about a week, the ligated sciatic nerve becomes irritated and reaches a hyper-responsive "kindled" state, where it will respond rapidly to even a mild stimulus that is not painful to an untampered leg. As such, it offers a model of what happens in pain pathways that have become pathologically hypersensitized in a human suffering from neuropathic pain.

In these tests, on the 8th day after surgery, the rat is placed in a testing device which electronically measures how quickly or slowly it acts, in lifting up a paw in response to a standardized mild warming (thermal) stimulus. The warming stimulus is generated by a light beam which shines onto the bottom surface of the paw, through the glass floor of the testing enclosure. The device is electronically controlled and automated, and measurements are made of the number of seconds that elapse after the light beam begins to shine on the bottom of the paw, until the rat lifts its paw.

To ensure that the surgical operation itself did not affect the outcomes, comparative tests using each dosage level were also carried out on control populations of "sham-operated" animals. These animals were subjected to the same type of anesthesia and incisions on one limb, but no loop of suture material was placed around the sciatic nerve.

In all animals, the other hind limb was not operated on, and provided an additional control, generated by the same animal.

The results of these control experiments (not shown) demonstrated that sham-operated limbs in control animals, and unoperated limbs in test animals, responded identically to the thermal stimulus, under all treatment conditions.

To establish baseline values for pain sensitivity of each limb in each group of animals, each limb was tested initially for thermal pain sensitivity before the ligation operation was performed (pre-surgery). After 8 days, each limb was again tested before any drug treatment was administered (shown by the "pre-treatment" legend in all graphs). After drug administration, each limb was tested for thermal pain sensitivity at hourly intervals, for 4 hours.

Saline controls and all drugs were administered by intraperitoneal (IP) injection, i.e., hypodermic injection into the abdominal region. This is a convenient and reliable method of drug administration, for tests involving rats.

The test results are shown graphically in the Figures; each circle indicates the mean

value, and the vertical bars show the standard error of the mean (SEM). In these graphs, the vertical position of each open circle indicates how many seconds elapsed (on average) between the commencement of the light beam which warmed the lower surface of the foot, and the act of lifting the hyper-sensitized hindpaw having the ligated nerve; by comparison, the vertical position of each darkened circle indicates how many seconds elapsed (on average) between the beginning of the thermal stimulus and lifting of the hind paw of the unoperated limb. Accordingly, a large vertical separation between a light circle (nerve-ligated paw) and a dark circle (control paw) indicates that the test animals were not well protected against neuropathic pain by the drug(s) used, at that dosage. By contrast, closely aligned dark and light circles indicate that the test animals were effectively protected against neuropathic pain by the drug(s) at the indicated dosage(s), at that point in time.

Large vertical gaps, showing a lack of effective pain control, are clearly indicated by the use of saline controls to test nerve-ligated animals, as shown in Fig. 1. Failure of the open circles to move vertically upward at any post-treatment interval, in a manner which reduced or closed the gap between the open circles and the dark circles, indicates that the inactive saline treatment did not provide any protection against neuropathic pain, in the nerve-ligated limb.

EXAMPLE 2: CLONIDINE ALONE

Clonidine also was tested at several dosages, by itself, using the same procedures described in Example 1. The graphs in Figs. 2A, 2B and 2C show the pain sensitivity in each limb when the treatment used was IP injection of clonidine at 0.025 mg/kg, 0.05 mg/kg or 0.075 mg/kg, respectively.

At the two lower doses (0.025 mg/kg and 0.05 mg/kg), clonidine showed no significant relief of neuropathic pain.

At the highest dose tested (0.075 mg/kg), significant and relatively sustained neuropathic pain relief was shown. However, at that dosage, the rats displayed significant sedation. In humans, a comparable dose would very likely produce both severe sedation, and a lowering of blood pressure to an unacceptable and potentially dangerous degree.

EXAMPLE 3: NMDA ANTAGONISTS ALONE

The graphs in FIGS. 3, 4, and 5 show the results of IP injection of one of the selected NMDA antagonists, by itself, at various dosages shown on the graphs. All of these

results indicate either little or no beneficial and/or prolonged relief from pain, as described above. The highest dosage of each drug tested was deliebrately chosen to be a dosage that would provoke problems of side effects, such as sedation, impairments to motor control or memory, etc.

EXAMPLE 4: COMBINATION OF CLONIDINE WITH NMDA ANTAGONIST

Using the same testing procedures described above, the effects of co-administering clonidine together with one of the NMDA antagonist drugs, at low dosages, are shown in FIGS. 6 through 8. All of these graphs show that when the two classes of drugs were administered together, the combination was far more effective than either drug by itself, in providing sustained relief from neuropathic pain. In all such tests, each drug was administered at a dose that, by itself, did not offer any substantial pain relieving effects.

EXAMPLE 5: REFLEX TESTING TO CONFIRM HINDPAW CONTROL

In the experiments described in Examples 1-4, above, eight days after the rats had undergone surgical placement of a ligature around the sciatic nerve, and before they were subjected to drug treatment or a thermal pain stimulus, each animal was tested for the presence of certain types of reflexes that must be intact in order for the rat to promptly lift its paw in response to a stimulus.

One such evaluation is performed by holding the animal by its torso, with its lower limbs hanging downward, and bringing the top surface of a hind paw in contact with the edge of a table top. All animals with an intact placing reflex will immediately lift its hindpaw and place it on top of the table, in response to this stimulus. Performance of this test ensures that the ligature around the sciatic nerve has not impaired the animal's ability to lift its paw. If any animal was unable to perform that function without impairment, it was removed from further testing.

EXAMPLE 6: ADDITIONAL TESTS TO EVALUATE ADVERSE SIDE EFFECTS

Studies were performed on separate groups of rats (not used in the pain testing sessions), to determine whether drug treatments at the doses administered in Examples 2-4 would produce detectable impairments to reflex response, motor control, or behavior. These studies helped clarify whether the drug dosages that proved successful in relieving neuropathic pain might produce adverse side effects that would preclude using this drug

combination in humans for the relief of chronic pain.

To address these issues, rats with sciatic nerve ligations, and rats with only sham sciatic nerve ligations, were treated with various doses of an NMDA antagonist (procyclidine, ethopropazine, or memantine) or clonidine, or the two agents together. They were then evaluated, using the following battery of sensorimotor and activity tests:

Sensorimotor Battery: Testing was done at 1 hour post-treatment, which corresponded with the time of peak effect of drugs on paw withdrawal latency. Briefly, the sensorimotor battery consisted of five tests (Wozniak et al 1990) that are known to be able to detect significant muscle weakness, incoordination, somnolence, or other behavioral impairments.

For all of the tests in this sensorimotor battery, all treatment groups first received a habituation trial, to allow each rat to acclimate to the test situation. In all tests, protective padding was placed under any elevated apparatuses, to prevent pain or injury from falling. The tests performed were as follows:

(1) Plank test. A rat was timed for how long it could remain on a wooden plank that is 3 cm wide, elevated 61 cm above the floor.

(2) Walking initiation (also a test of sedation and activity level). Each rat was placed in the middle of a square outlined by white cloth tape (50x50 cm) on a smooth black surface of a large table top, and was timed for how long was required for the rat to leave the square (place all four paws outside the square).

(3) Platform. Each rat was timed for how long it could remain perched on an elevated (61 cm above the floor) platform of small dimensions (7.6 x 15.2 cm).

(4) Inclined screen. Each rat was placed in the middle of an elevated (61 cm above the floor) wire mesh grid (8 squares per 10 cm) which was inclined at 60 degrees with the floor. The rat's head was oriented downward toward the floor, and it was timed for how long it could continue to hold onto the screen.

(5) One hour activity level. Locomotor activity was evaluated beginning at 0.5 hr following drug treatment, and lasting for 1 hr. In this test, the rat was placed in a cage equipped with three pairs of photoelectric cells, placed at regular intervals across the width of the cage, so that the animal's activity was monitored by automatically recording the number of "beam breaks" registered as the animal moved about the cage.

The results indicated that clonidine, administered by itself at a dose of 0.050 mg/kg, did reduce activity levels, but only slightly and to a barely significant degree. At a dose of

0.075 mg/kg, clonidine substantially reduced activity levels, indicating that at that does, it had substantial sedating effects.

None of the combined NMDA antagonist-plus-clonidine treatment regimens that proved effective for relieving neuropathic pain was associated with any impaired performance on any of the above described sensorimotor tests.

Thus, there has been shown and described a new and useful combined drug treatment for reducing neuropathic and/or other chronic pain. Although this invention has been exemplified for purposes of illustration and description by reference to certain specific embodiments, it will be apparent to those skilled in the art that various modifications, alterations, and equivalents of the illustrated examples are possible. Any such changes which derive directly from the teachings herein, and which do not depart from the spirit and scope of the invention, are deemed to be covered by this invention.

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CLAIMS

1. In the preparation of a medicament for treating chronic pain, the step of combining:

(a) a first drug which suppresses activity at NMDA-type glutamate receptors; and,

(b) a second drug which stimulates activity at alpha-2 adrenergic receptors,

wherein the first and second drugs are provided in the medicament at dosages or concentrations which (i) provide synergistic and therapeutically effective relief from chronic pain, and (ii) are sufficiently low that they will not cause unacceptable adverse side effects.

2. The invention of claim 1, wherein the first drug is an aryl-cyclo-alkanol-amine compound selected from the group consisting of procyclidine, biperiden, triperiden, trihexyphenydyl, glycopyrrolate, hexocylium, oxyphenonium, tridihexethyl, oxyphencyclomine, mepenzolate, piperodolate, isopropamide, thiphenamil, adiphenine, and dicyclomine, and prodrugs, salts, isomers, analogs and derivatives thereof which are pharmaceutically acceptable, and which suppresses activity at NMDA-type glutamate receptors.

3. The invention of claim 1, wherein the first drug is a tricyclic-alkylamine selected from the group consisting of phenothiazine-alkylamines, thioxanthene-alkylamines, xanthene-alkylamines, dibenzo-cyclohexyl-alkylamines, dibenzo-cycloheptene-alkylamines, and prodrugs, salts, isomers, analogs and derivatives thereof which are pharmaceutically acceptable, and which suppresses activity at NMDA-type glutamate receptors.

4. The invention of claim 1, wherein the first drug is an adamantane derivative selected from the group consisting of memantine, and prodrugs, salts, isomers, analogs and derivatives thereof which are pharmaceutically acceptable and which suppresses activity at NMDA-type glutamate receptors.

5. The invention of claim 1, wherein the second drug is selected from the group consisting of clonidine, iodoclonidine, guanabenz, guanfacine, xylazine, lofexidine, medetomidine, dexmedetomidine, tizanidine, rilmenidine, azepexole, α-methyldopa, and α-

methylnoradrenaline, and prodrugs, salts, isomers, analogs and derivatives thereof which are pharmacologically acceptable, and which stimulate activity at $\alpha 2$ adrenergic receptors.

6. The invention of claim 1, wherein the medicament is suited for administration in a painless manner that does not require a hypodermic injection.

7. The invention of claim 1, wherein the medicament is suited for oral ingestion.

8. The invention of claim 1, wherein the medicament is suited for transmembrane permeation.

9. A pharmacological preparation suited for daily treatment of chronic pain, comprising a combination of:

(a) a first drug which suppresses activity at NMDA-type glutamate receptors; and,

(b) a second drug which stimulates activity at alpha-2 adrenergic receptors,

wherein the first and second drugs are provided in the mixture at dosages or concentrations which (i) provide synergistic and therapeutically effective relief from chronic pain, and (ii) are sufficiently low that they will not cause unacceptable adverse side effects.

10. The pharmacological preparation of Claim 9 wherein the first drug is an aryl-cyclo-alkanol-amine compound selected from the group consisting of procyclidine, biperiden, triperiden, trihexyphenydyl, glycopyrrolate, hexocylium, oxyphenonium, tridihexethyl, oxyphencyclomine, mepenzolate, piperodolate, isopropamide, thiphenamil, adiphenine, and dicyclomine, and prodrugs, salts, isomers, analogs and derivatives thereof which are pharmaceutically acceptable, and which suppresses activity at NMDA-type glutamate receptors.

11. The pharmacological preparation of Claim 9 wherein the first drug is a tricyclic-alkylamine selected from the group consisting of phenothiazine-alkylamines, thioxanthene-alkylamines, xanthene-alkylamines, dibenzo-cyclohexyl-alkylamines, dibenzo-cycloheptene-alkylamines, and prodrugs, salts, isomers, analogs and derivatives thereof which are pharmaceutically acceptable, and which suppresses activity at NMDA-type glutamate receptors.

12. The pharmacological preparation of Claim 9 wherein the first drug is an adamantane derivative selected from the group consisting of memantine, and prodrugs, salts, isomers, analogs and derivatives thereof which are pharmaceutically acceptable and which suppresses activity at NMDA-type glutamate receptors.

13. The pharmacological preparation of Claim 9 wherein the second drug is selected from the group consisting of clonidine, iodoclonidine, guanabenz, guanfacine, xylazine, lofexidine, medetomidine, dexmedetomidine, tizanidine, rilmenidine, azepexole, α-methyldopa, and α-methylnoradrenaline, and salts, isomers, analogs and derivatives thereof which are pharmacologically acceptable, and which stimulate activity at α2 adrenergic receptors.

14. The pharmacological preparation of Claim 9 wherein the first drug and the second drug are both present in a unitary dosage form.

15. The pharmacological preparation of Claim 14 wherein the unitary dosage form is designed for oral ingestion.

16. The pharmacological preparation of Claim 14 wherein the unitary dosage form is selected from the group consisting of tablets and capsules.

17. The pharmacological preparation of Claim 14 wherein the unitary dosage form comprises a skin patch.

18. The pharmacological preparation of claim 14, wherein the unitary dosage form is provided by controlled concentrations of the first drug and the second drug in a nondivided material selected from the group consisting of liquids, aerosols, and powders.

19. The pharmacological preparation of claim 18, wherein the nondivided material is packaged in a dispensing device that is capable of dispensing a predetermined volume of the nondivided material each time the device is used.

FIG. 1

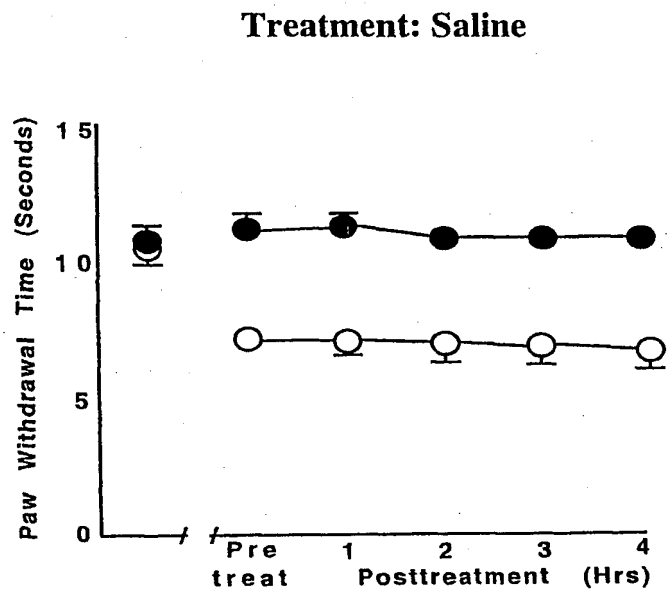
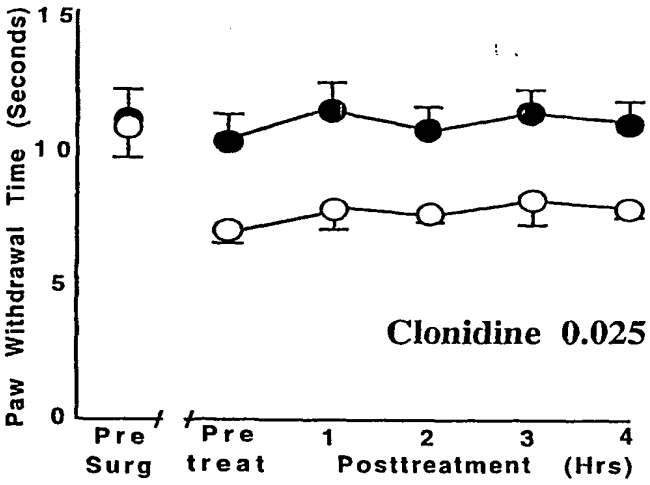


FIG. 2

CLONIDINE ALONE

Unoperated Limb ●
Ligated Limb ○

A



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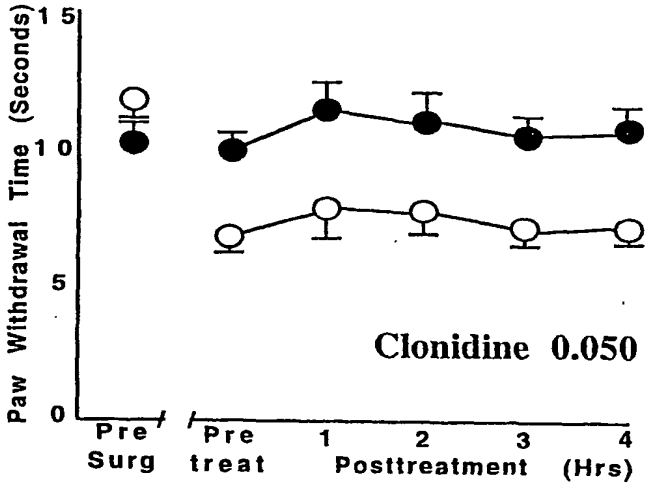

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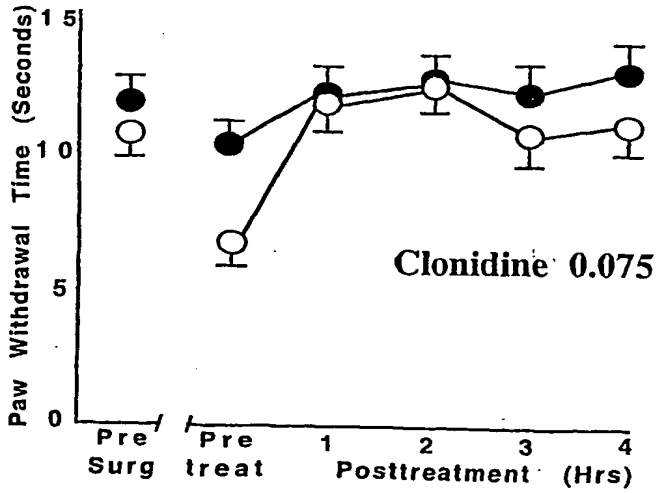


FIG. 3

PROCYCLIDINE ALONE

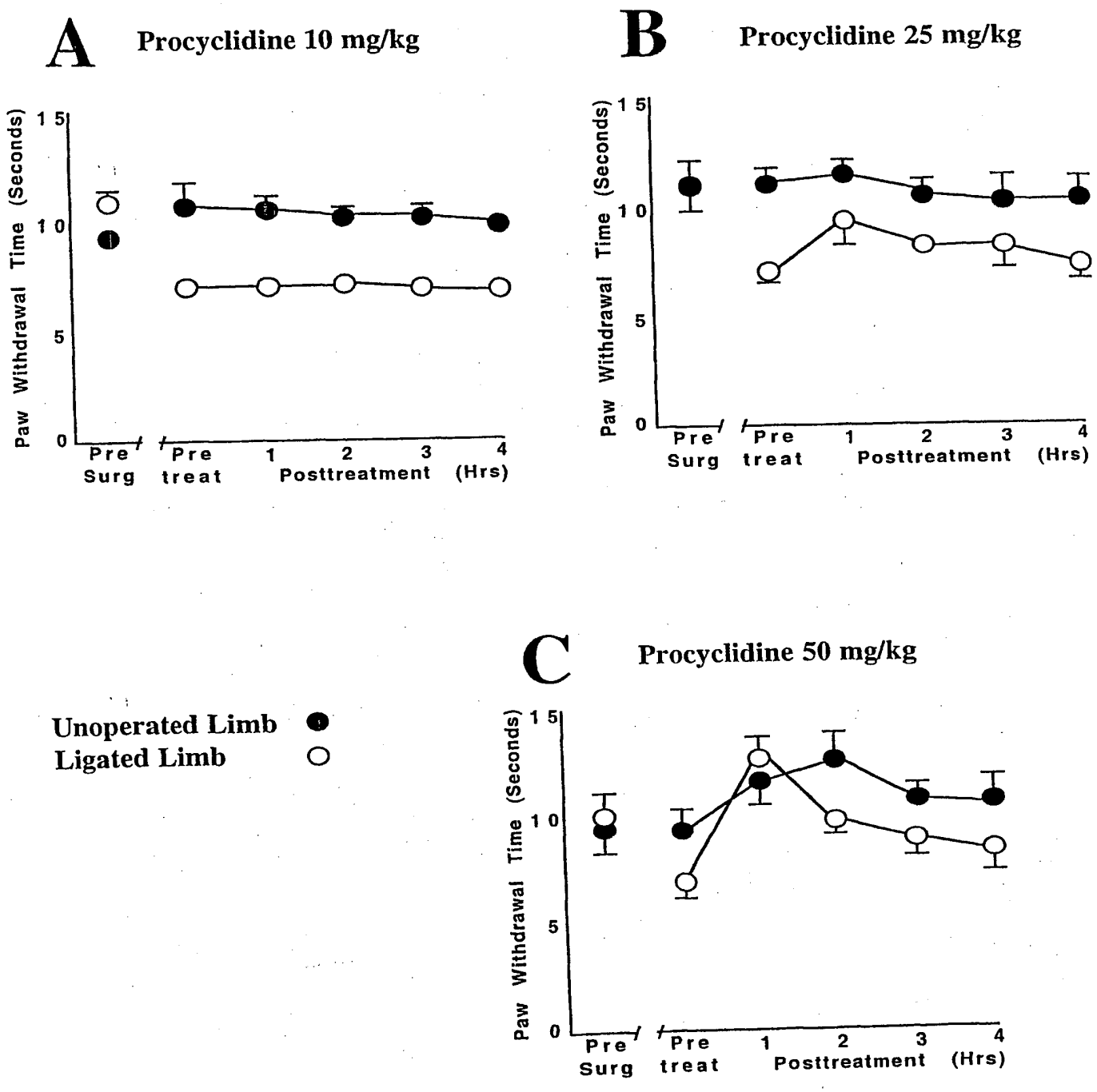


FIG. 4

ETHOPROPAZINE ALONE

Unoperated Limb ●
Ligated Limb ○

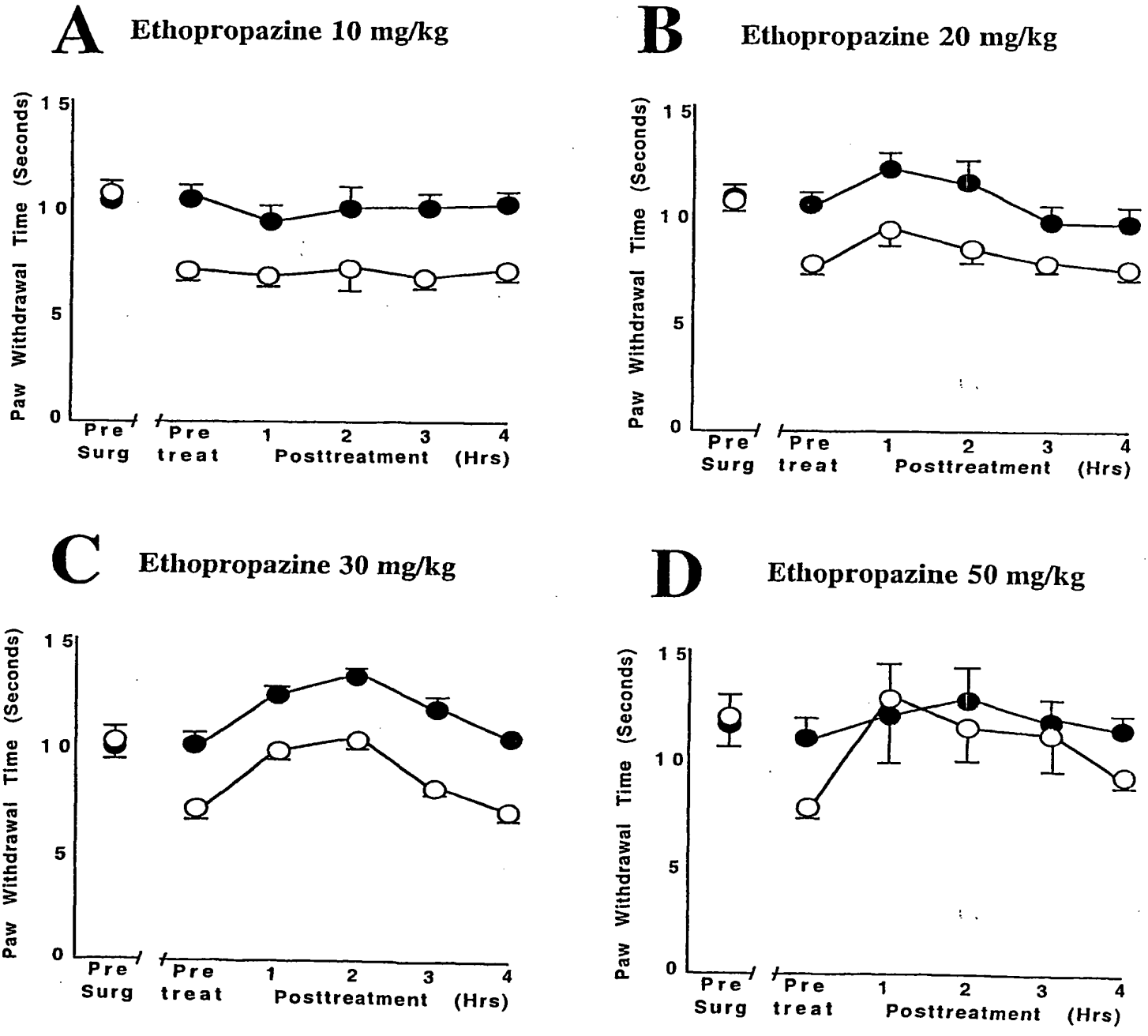
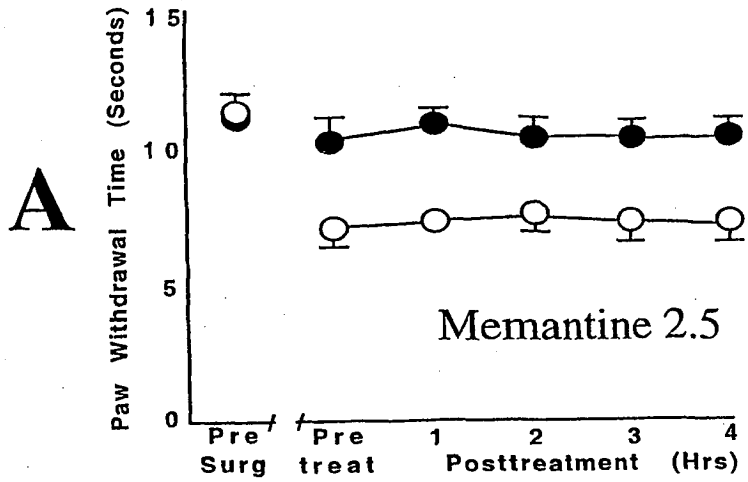
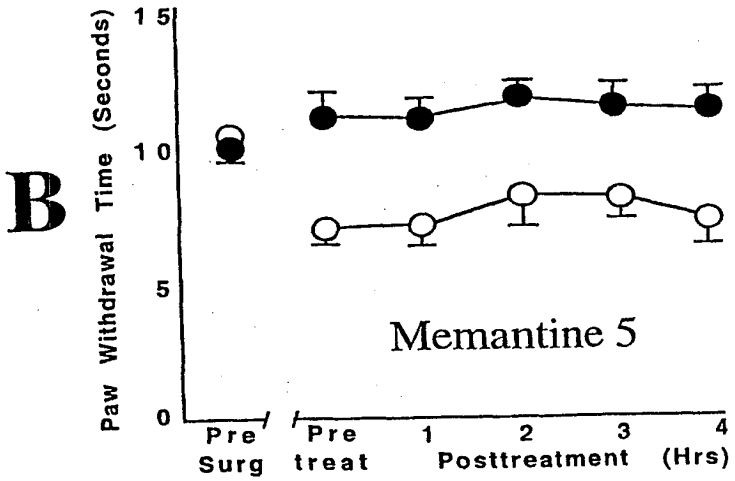


FIG. 5

MEMANTINE ALONE

Unoperated Limb ●
Ligated Limb ○





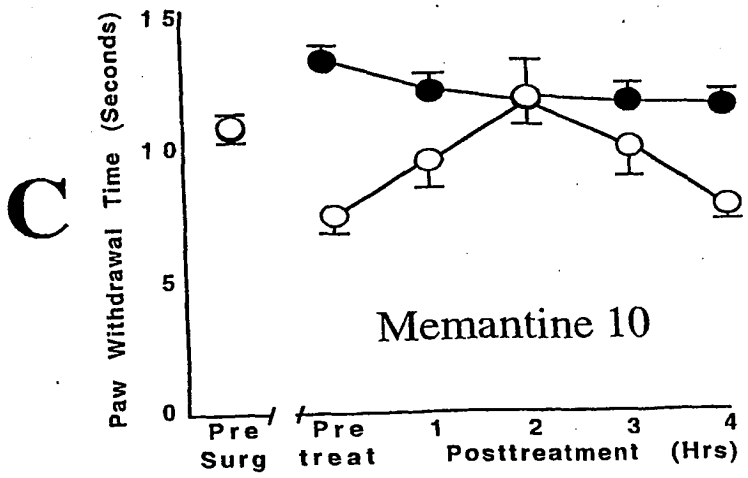
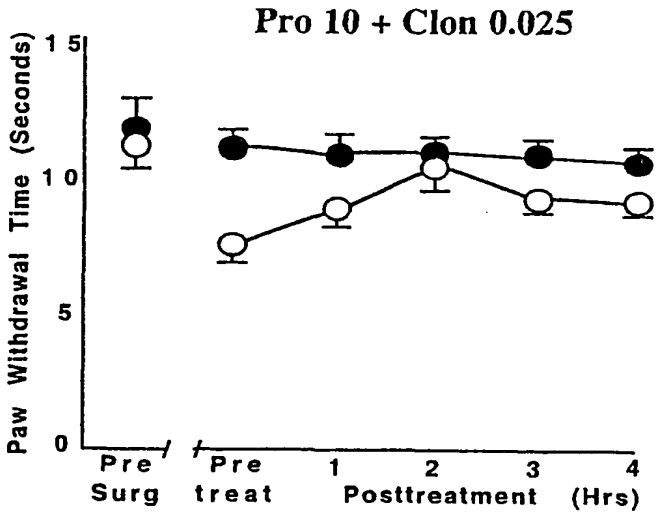


FIG. 6

PROCYCLIDINE & CLONIDINE COMBINED

A



B

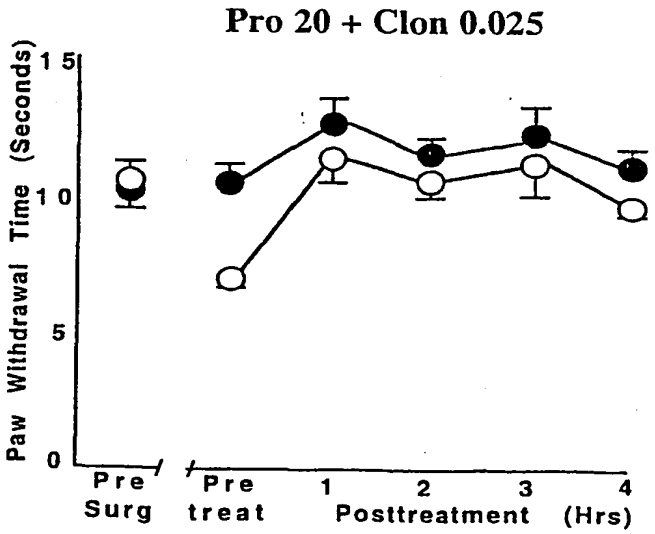
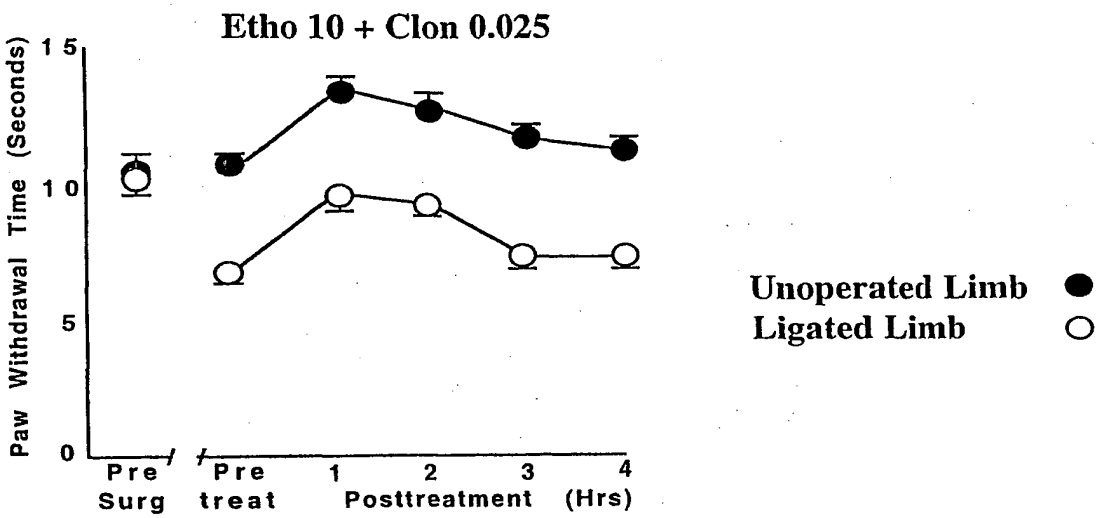


FIG. 7

ETHOPROPAZINE & CLONIDINE COMBINED

A



B

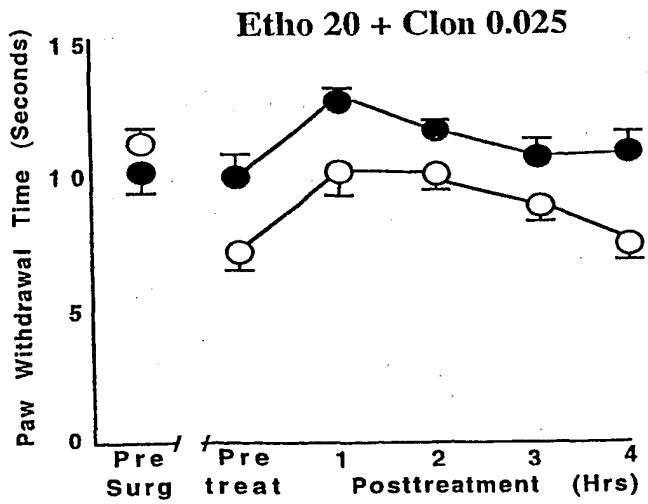
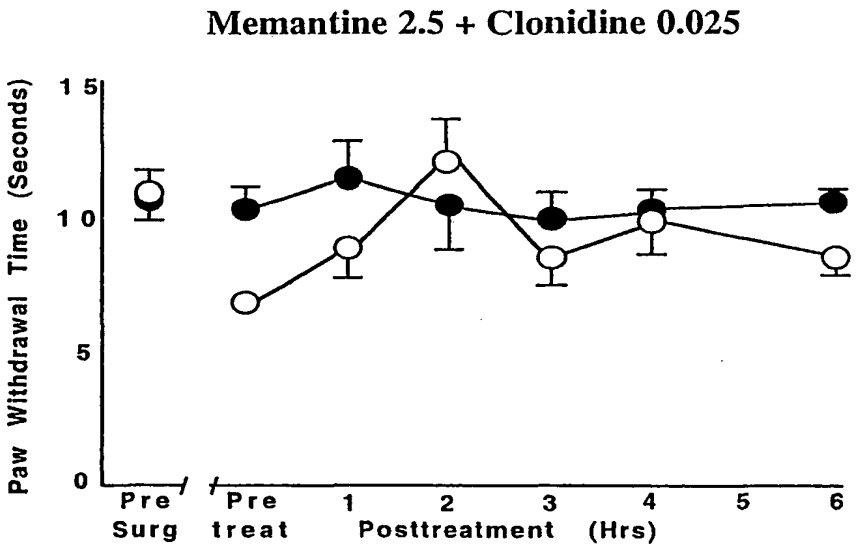


FIG. 8

MEMANTINE & CLONIDINE COMBINED



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(54) Title: COMBINATION OF ADRENERGIC AGONIST AND NMDA ANTAGONIST FOR RELIEVING CHRONIC PAIN WITHOUT ADVERSE SIDE EFFECTS

(57) Abstract: A combination of two drugs, from different and unrelated categories, provides effective and long-lasting relief from neuropathic pain and other chronic or intractable pain. Both drugs can be taken in a painless non-invasive manner, such as by means of pills or skin patches. One drug is an α2 adrenergic agonist, exemplified by clonidine. These agents reduce blood pressure and have sedative-hypnotic effects; those are unwanted side effects in a chronic daily treatment for pain. The other drug is an NMDA antagonist which can be described as mild, minimally toxic, and/or inherently safe (or safened). Three such classes of drugs have been shown to work exceptionally well, with clonidine, in reducing neuropathic pain for prolonged periods: (1) aryl-cyclo-alkanolamine drugs such as procyclidine and biperiden; (2) tricyclo-alkylamine drugs such as ethopropazine; and (3) adamantane derivatives such as memantine. None of these drugs, by itself, can provide effective relief for neuropathic pain; at doses required to provide short-term relief, they cause adverse side effects, and any pain relief they provide is relatively brief. However, when combined with an α2 adrenergic agonist, the two drugs potentiate one another's pain-relieving action, and provide potent and sustained relief, even when each drug is administered at a low dosage that is below its threshold for causing adverse side effects.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/54, 31/55, 31/445

US CL :514/214, 226.2, 315, 318, 646

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST: USPAT, EPOABS; STN: CAPLUS, EMBASE, BIOSIS, WPIDS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,925,634 A (OLNEY, J.W.) 20 July 1999, see entire document, especially abstract; col. 3-7; col. 12-15; patent claims, especially claims 4-5.	1, 4, 5, 9, 12-19
X	US 5,980,927 A (NELSON et al.) 09 November 1999, see entire document, especially abstract; col. 1-2, col. 4, and document claims, especiall claims 1, 7, 8-10.	1, 5-9 and 13-19
X --- Y	US 5,605,911 A (OLNEY et al.) 25 February 1997, see entire document, especially abstract; col. 3-6; col. 10-12; col. 18-21; and document claims 1-20	1,2,4-10,12-19 --------- 3 and 11
Y	US 4,833,138 A (OLNEY, J.W.) 23 May 1989, see entire document, especially abstract; and col. 2-3	3 and 11

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,502,049 A (GARRET et al.) 26 March 1996, see entire document.	1-19

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